PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : **A61K 38/00, 38/02, C07K 5/00, 7/00**	A2	(11) International Publication Number: **WO 98/51325** (43) International Publication Date: 19 November 1998 (19.11.98)

(21) International Application Number: PCT/US98/10088

(22) International Filing Date: 15 May 1998 (15.05.98)

(30) Priority Data:
60/046,595 15 May 1997 (15.05.97) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 60/046,595 (CIP)
Filed on 15 May 1997 (15.05.97)

(71) Applicants *(for all designated States except US)*: CYTOGEN CORPORATION [US/US]; 600 College Road East, Princeton, NJ 08540 (US). ELAN CORPORATION, PLC [IE/IE]; Lincoln House, Lincoln Place, Dublin 2 (IE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ALVAREZ, Vernon, L. [US/US]; 187 Rice Drive, Morrisville, PA 19067 (US). O'MAHONY, Daniel, J. [IE/IE]; 75 Avoca Park, Avoca Avenue, Blackrock, Dublin (IE). LAMBKIN, Imelda, J. [IE/IE]; 9 Station Road, Sutton, Dublin 13 (IE). PATTERSON, Catherine, A. [GB/IE]; 3 Grange Crescent, Pottery Road, Dunlaoghaire, Dublin (IE). SINGLETON, Judith [US/US]; Knoll Way, Rocky Way, NJ 08553 (US). BELINKA, Benjamin, A., Jr. [US/US]; 15 Pelham Road, Kendall Park, NJ 08824 (US). CARTER, John, M. [US/US]; 35 Chicory Lane, Trenton, NJ 08638-1926 (US). CAGNEY, Gerard, M. [IE/US]; 2618 Yale Avenue East, Seattle, WA 98102 (US).

(74) Agents: ANTLER, Adriane, M. et al.; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US).

(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, GW, HU, ID, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: RANDOM PEPTIDES THAT BIND TO GASTRO-INTESTINAL TRACT (GIT) TRANSPORT RECEPTORS AND RELATED METHODS

(57) Abstract

This invention relates to proteins (e.g., peptides) that are capable of facilitating transport of an active agent through a human or animal gastro-intestinal tissue, and derivatives (e.g., fragments) and analogs thereof, and nucleotide sequences coding for said proteins and derivatives. The proteins of the invention have use in facilitating transport of active agents from the lumenal side of the GIT into the systemic blood system, and/or in targeting active agents to the GIT. Thus, for example, by binding (covalently or noncovalently) a protein of the invention to an orally administered drug, the drug can be targeted to specific receptor sites or transport pathways which are known to operate in the human gastro-intestinal tract, thus facilitating its absorption into the systemic system.

```
                  20                   40                   60
MGMSKSHSFFGYPLSIFFIV VNEFCERFSYYGMRAILILY FTNFISWDDNLSTAIYHTFV

                  80                  100                  120
ALCYLTPILGALIADSWLGK FKTIVSLSIVYTIGQAVTSV SSINDLTDHNHDGTPDSLPV

                 140                  160                  180
HVVLSLIGLALIALGTGGIK PCVSAFGGDQFEEGQEKQRN RFFSIFYLAINAGSLLSTII

                 200                  220                  240
TPMLRVQQCGIHSKQACYPL AFGVPAALMAVALIVFVLGS GMYKKFKPQGNIMGKVAKCI

                 260                  280                  300
GFAIKNRFRHRSKAFPKREH WLDWAKEKYDERLISQIKMV TRVMFLYIPLPMFWALFDQQ

                 320                  340                  360
GSRWTLQATTMSGKIGALEI QPDQMQTVNAILIVIMVPIF DAVLYPLIAKCGFNFTSLKK

                 380                  400                  420
MAVGMVLASMAFVVAAIVQV EIDKTLPVFPKGNEVQIKVL NIGNNTMNISLPGEMVTLGP

                 440                  460                  480
MSQTNAFMTFDVNKLTRINI SSPGSPVTAVTDDFKQGQRH TLLVWAPNHYQVVKDGLNQK

                 500                  520                  540
PEKGENGIRFVNTFNELITI TMSGKVYANISSYNASTYQF FPSGIKGFTISSTEIPPQCQ

                 560                  580                  600
PNFNTFYLEFGSAYTYIVQR KNDSCPEVKVFEDISANTVN MALQIPQYFLLTCGEVVFSV

                 620                  640                  660
TGLEFSYSQAPSNMKSVLQA GWLLTVAVGNIIVLIVAGAG QFSKQWAEYILFAALLLVVC

                 680                  700      708
VIFAIMARFYTYINPAEIEA QFDEDEKKNRLEKSNPYFMS GANSQKQM
```

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

RANDOM PEPTIDES THAT BIND TO GASTRO-INTESTINAL TRACT (GIT) TRANSPORT RECEPTORS AND RELATED METHODS

This application claims priority to U.S. provisional application Serial No. 60/046,595 filed May 15, 1997, which is incorporated by reference herein in its entirety.

1. INTRODUCTION

The present invention relates generally to random peptides capable of specific binding to gastro-intestinal tract (GIT) transport receptors. In particular, this invention relates to peptide sequences and motifs, as well as derivatives thereof, which enhance drug delivery and transport through tissue, such as epithelial cells lining the lumenal side of the gastro-intestinal tract (GIT). Production of peptides, derivatives and antibodies is also provided. The invention further relates to pharmaceutical compositions, formulations and related methods.

2. BACKGROUND OF THE INVENTION

2.1. Peptide Libraries

There have been two different approaches to the construction of random peptide libraries. According to one approach, peptides have been chemically synthesized *in vitro* in several formats. Examples of chemically synthesized libraries can be found in Fodor, S., et al., 1991, Science 251: 767-773; Houghten, R., et al., 1991, Nature 354: 84-86; and Lam, K., et al., 1991, Nature 354: 82-84.

A second approach to the construction of random peptide libraries has been to use the M13 phage, and, in particular, protein pIII of M13. The viral capsid protein of M13, protein III (pIII), is responsible for infection of bacteria. Several investigators have determined from mutational analysis that the 406 amino acid long pIII capsid

protein has two domains. The C-terminus anchors the protein to the viral coat, while portions of the N-terminus of pIII are essential for interaction with the *E. coli* pillin protein (Crissman, J.W. and Smith, G.P., 1984, Virology 132: 445-455). Although the N-terminus of the pIII protein has shown to be necessary for viral infection, the extreme N-terminus of the mature protein does tolerate alterations. In 1985, George Smith published experiments reporting the use of the pIII protein of bacteriophage M13 as an experimental system for expressing a heterologous protein on the viral coat surface (Smith, G.P., 1985, Science 228: 1315-1317). It was later recognized, independently by two groups, that the M13 phage pIII gene display system could be a useful one for mapping antibody epitopes (De la Cruz, V., et al., 1988, J. Biol. Chem. 263: 4318-4322; Parmley, S.F. and Smith, G.P., 1988, Gene 73: 305-318).

Parmley, S.F. and Smith, G.P., 1989, Adv. Exp. Med. Biol. 251: 215-218 suggested that short, synthetic DNA segments cloned into the pIII gene might represent a library of epitopes. These authors reasoned that since linear epitopes were often ~6 amino acids in length, it should be possible to use a random recombinant DNA library to express all possible hexapeptides to isolate epitopes that bind to antibodies. Scott, J.K. and Smith, G.P., 1990, Science 249: 386-390 describe construction and expression of an "epitope library" of hexapeptides on the surface of M13. Cwirla, S.E., et al., 1990, Proc. Natl. Acad. Sci. USA 87: 6378-6382 also described a somewhat similar library of hexapeptides expressed as gene pIII fusions of M13 fd phage. PCT Application WO 91/19818 published December 26, 1991 by Dower and Cwirla describes a similar library of pentameric to octameric random amino acid sequences. Devlin et al., 1990, Science, 249: 404-406, describes a peptide library of about 15 residues generated using an (NNS) coding scheme for oligonucleotide synthesis in which S is G or C. Christian and colleagues have described a phage display library,

expressing decapeptides (Christian, R.B., et al., 1992, J. Mol. Biol. 227: 711-718).

Other investigators have used other viral capsid proteins for expression of non-viral DNA on the surface of phage particles. For example, the major capsid protein pVIII was so used by Cesareni, G., 1992, FEBS Lett. 307: 66-70. Other bacteriophage than M13 have been used to construct peptide libraries. Four and six amino acid sequences corresponding to different segments of the *Plasmodium falciparum* major surface antigen have been cloned and expressed in the filamentous bacteriophage fd (Greenwood, J., et al., 1991, J. Mol. Biol. 220: 821-827).

Kay et al., 1993, Gene 128: 59-65 (Kay) discloses a method of constructing peptide libraries that encode peptides of totally random sequence that are longer than those of any prior conventional libraries. The libraries disclosed in Kay encode totally synthetic random peptides of greater than about 20 amino acids in length. Such libraries can be advantageously screened to identify peptides, polypeptides and/or other proteins having binding specificity for a variety of ligands. (See also U.S. Patent No. 5,498,538 dated March 12, 1996; and PCT Publication No. WO 94/18318 dated August 18, 1994.)

A comprehensive review of various types of peptide libraries can be found in Gallop et al., 1994, J. Med. Chem. 37:1233-1251.

Screening of peptide libraries has often been done using an antibody as ligand (Parmley and Smith, 1989, Adv. Exp. Med. Biol. 251:215-218; Scott and Smith, 1990, Science 249:386-390). In many cases, the aim of the screening is to identify peptides from the library that mimic the epitopes to which the antibodies are directed. Thus, given an available antibody, peptide libraries are excellent sources for identifying epitopes or epitope-like molecules of that antibody (Yayon et al., 1993, Proc. Natl. Acad. Sci. USA 90:10643-10647).

McCafferty et al., 1990, Nature 348:552-554 used PCR to amplify immunoglobulin variable (V) region genes and cloned those genes into phage expression vectors. The authors suggested that phage libraries of V, diversity (D), and joining (J) regions could be screened with antigen. The phage that bound to antigen could then be mutated in the antigen-binding loops of the antibody genes and rescreened. The process could be repeated several times, ultimately giving rise to phage which bind the antigen strongly.

Marks et al., 1991, J. Mol. Biol. 222:581-597 also used PCR to amplify immunoglobulin variable (V) region genes and cloned those genes into phage expression vectors.

Kang et al., 1991, Proc. Natl. Acad. Sci. USA 88:4363-4366 created a phagemid vector that could be used to express the V and constant (C) regions of the heavy and light chains of an antibody specific for an antigen. The heavy and light chain V-C regions were engineered to combine in the periplasm to produce an antibody-like molecule with a functional antigen binding site. Infection of cells harboring this phagemid with helper phage resulted in the incorporation of the antibody-like molecule on the surface of phage that carried the phagemid DNA. This allowed for identification and enrichment of these phage by screening with the antigen. It was suggested that the enriched phage could be subject to mutation and further rounds of screening, leading to the isolation of antibody-like molecules that were capable of even stronger binding to the antigen.

Hoogenboom et al., 1991, Nucleic Acids Res. 19:4133-4137 suggested that naive antibody genes might be cloned into phage display libraries. This would be followed by random mutation of the cloned antibody genes to generate high affinity variants.

Bass et al., 1990, Proteins: Struct. Func. Genet. 8:309-314 fused human growth hormone (hGH) to the carboxy terminus of the gene III protein of phage fd. This fusion protein was built into a phagemid vector. When cells carrying the phagemid were infected with a helper phage,

about 10% of the phage particles produced displayed the fusion protein on their surfaces. These phage particles were enriched by screening with hGH receptor-coated beads. It was suggested that this system could be used to develop mutants of hGH with altered receptor binding characteristics.

Lowman et al., 1991, Biochemistry 30:10832-10838 used an improved version of the system of Bass et al. described above to select for mutant hGH proteins with exceptionally high affinity for the hGH receptor. The authors randomly mutagenized the hGH-pIII fusion proteins at sites near the vicinity of 12 amino acids of hGH that had previously been identified as being important in receptor binding.

Balass et al., 1993, Proc. Natl. Acad. Sci. USA 90:10638-10642 used a phage display library to isolate linear peptides that mimicked a conformationally dependent epitope of the nicotinic acetylcholine receptor. This was done by screening the library with a monoclonal antibody specific for the conformationally dependent epitope. The monoclonal antibody used was thought to be specific to the acetylcholine receptor's binding site for its natural ligand, acetylcholine.

2.2. Drug Delivery Systems

The common routes of therapeutic drug administration are oral ingestion or parenteral (intravenous, subcutaneous and intramuscular) routes of administration. Intravenous drug administration suffers from numerous limitations, including (i) the risk of adverse effects resulting from rapid accumulation of high concentrations of drug, (ii) repeated injections which can cause patient discomfort; and (iii) the risk of infection at the site of repeated injections. Subcutaneous injection is not generally suitable for delivering large volumes or for irritating substances. Whereas oral administration is generally more convenient, it is limited where the therapeutic agent is not efficiently absorbed by the gastrointestinal tract. To date,

the development of oral formulations for the effective delivery of peptides, proteins and macromolecules has been an elusive target. Poor membrane permeability, enzymatic instability, large molecular size, and hydrophilic properties are four factors that have remained major hurdles for peptide and protein formulations (reviewed by Fix, J.A., 1996, J. Pharmac. Sci. 85:1282-1285). In order to develop an efficacious oral formulation, the peptide must be protected from the enzymatic environment of the gastrointestinal tract (GIT), presented to the absorptive epithelial barrier in a sufficient concentration to effect transcellular flux (Fix, J.A., 1996, J. Pharmac. Sci. 85:1282-1285), and if possible "smuggled" across the epithelial barrier in an apical to basolateral direction.

Site specific drug delivery or drug targeting can be achieved at different levels, including (i) primary targeting to a specific organ, (ii) secondary targeting to a specific cell type within that organ and (iii) tertiary targeting where the drug is delivered to specific intracellular structures (*e.g.*, the nucleus for genes) (reviewed in Davis and Jllum, 1994, In: Targeting of Drugs 4, (Eds), Gregoriadis, McCormack and Poste, 183-194). At present there is a considerable amount of ongoing research work in the Drug Delivery Systems (DDS) area, and much of it addresses (i) targeting delivery and (ii) the development of non-invasive ways of getting macromolecules, peptides, proteins, products of the biotechnology industry, etc. into the body (Evers, P., 1995, Developments in Drug Delivery: Technology and Markets, Financial Times Management Report). It is generally accepted that targeted drug delivery is crucial to the improved treatment of certain diseases, especially cancer, and not surprisingly many of the approaches to targeted drug delivery are focused in the cancer area. Many anticancer drugs are toxic to the body as well as to malignant cells. If a drug, or a delivery system, can be modified so that it "homes in" on the tumor, then by maximizing the drug concentration at the disease site, the

anti-cancer effect can be exploited to the full, while toxicity is greatly reduced. Tumors contain antigens which provoke the body to respond by producing antibodies designed to attach to the antigens and destroy them. Monoclonal antibodies are being used as both delivery vehicles targeted to tumor cells (reviewed by Pietersz, G.A., 1990, Bioconjugate Chem. 1:89-95) and as imaging agents to carry molecules of drug or imaging agent to the tumor surface.

2.3. Transport Pathways

The epithelial cells lining the lumenal side of the GIT are a major barrier to drug delivery following oral administration. However, there are four recognized transport pathways which can be exploited to facilitate drug delivery and transport: the transcellular, paracellular, carrier-mediated, and transcytotic pathways. The ability of a conventional drug, peptide, protein, macromolecule or nano- or microparticulate system to "interact" with one of these transport pathways may result in increased delivery of that drug or particle from the GIT to the underlying circulation.

In the case of the receptor-mediated, carrier-mediated or transcytotic transport pathways, some of the uptake signals have been identified. These signals include, *inter alia*, folic acid, which interacts with the folate receptor, and cobalamin, which interacts with Intrinsic Factor. In addition, leucine- and tyrosine-based peptide sorting motifs or internalization sequences exist, such as YSKV, FPHL, YRGV, YQTI, TEQF, TEVM, TSAF, and YTRF (SEQ ID NOS:203, 204, 205, 206, 207, 208, 209, and 210, respectively), which facilitate uptake or targeting of proteins using specific membrane receptors or binding sites to identify peptides that bind specifically to the receptor or binding site.

Non-receptor based assays to discover particular ligands have also been used. For instance, a strategy for identifying peptides that alter cellular function by scanning whole cells with phage display libraries is disclosed in Fong

et al., Drug Development Research 33:64-70 (1994). However, because whole cells, rather than intact tissue or polarized cell cultures, are used for screening phage display libraries, this procedure does not provide information regarding sequences whose primary function includes affecting transport across polarized cell layers.

Additionally, Stevenson *et al.*, Pharmaceutical Res. 12(9), S94 (1995) discloses the use of Caco-2 monolayers to screen a synthetic tripeptide combinatorial library for information relating to the permeability of di- and tri-peptides.

A method of identifying a peptide which permits or facilitates the transport of an active agent through human or animal tissues has been developed (see U.S. patent application Serial No. 08/746,411 filed November 8, 1996, which is incorporated by reference herein in its entirety). Phage from a random phage library is plated onto or brought into contact with a first side, preferably the apical side, of a tissue sample, either *in vitro*, *in vivo* or *in situ*, or polarized tissue cell culture. The phage which is transported to a second side of the tissue opposite the first side, preferably the basolateral side, is harvested to select transported phages. The transported phages are amplified in a host and this cycle is repeated (using the transported phage from the most recent cycle) to obtain a selected phage library containing phage which can be transported from the first side to the second side.

Discussion or citation of a reference hereinabove shall not be construed as meaning that such reference is prior art to the present invention.

3. SUMMARY OF THE INVENTION

The present invention relates generally to random peptides and peptide motifs capable of specific binding to GIT transport receptors. Such proteins can be identified using any random peptide library, *e.g.*, a chemically synthesized peptide library or a biologically expressed

peptide library. If a biological peptide expression library is used, the nucleic acid which encodes the peptide which binds to the ligand of choice can be recovered, and then sequenced to determine its nucleotide sequence and hence deduce the amino acid sequence that mediates binding. Alternatively, the amino acid sequence of an appropriate binding domain can be determined by direct determination of the amino acid sequence of a peptide selected from a peptide library containing chemically synthesized peptides. In a less preferred aspect, direct amino acid sequencing of a binding peptide selected from a biological peptide expression library can also be performed.

In particular, this invention relates to proteins (*e.g.*, peptides) that are capable of facilitating transport of an active agent through a human or animal gastro-intestinal tissue, and derivatives (*e.g.*, fragments) and analogs thereof, and nucleotide sequences coding for said proteins and derivatives.

Preferably, the tissue through which transport is facilitated is of the duodenum, jejunum, ileum, ascending colon, transverse colon, descending colon, or pelvic colon. The tissue is most preferably epithelial cells lining the lumenal side of the GIT.

The proteins of the invention have use in facilitating transport of active agents from the lumenal side of the GIT into the systemic blood system, and/or in targeting active agents to the GIT. Thus, for example, by binding (covalently or noncovalently) a protein of the invention to an orally administered drug, the drug can be targeted to specific receptor sites or transport pathways which are known to operate in the human gastrointestinal tract, thus facilitating its absorption into the systemic system.

The invention also relates to derivatives and analogs of the invention which are functionally active, *i.e.*, they are capable of displaying one or more known functional activities associated with a full-length peptide. Such

functional activities include but are not limited to antigenicity (ability to bind or to compete with GIT transport receptor-binding peptides for binding to an anti-GIT transport receptor antibody) and ability to bind or compete with full-length peptide for binding to a GIT transport receptor.

The invention further relates to fragments of (and derivatives and analogs thereof) GIT transport receptor-binding peptides which comprise one or more motifs of a GIT transport receptor-binding peptide.

Antibodies to GIT transport receptor-binding peptides and GIT transport receptor-binding peptide derivatives and analogs are additionally provided.

Methods of production of the GIT transport receptor-binding peptides, derivatives, fragments and analogs, *e.g.*, by recombinant means, are also provided.

The present invention also relates to therapeutic methods, pharmaceutical compositions and formulations based on GIT transport receptor-binding peptides. Formulations of the invention include but are not limited to GIT transport receptor-binding peptides or motifs and derivatives (including fragments) thereof; antibodies thereto; and nucleic acids encoding the GIT transport receptor-binding peptides or derivatives associated with an active agent. Preferably, the active agent is a drug or drug-containing nano- or microparticle.

The GIT transport-receptor binding proteins of the invention can also be used to determine levels of the GIT transport receptors in a sample by binding thereto.

The GIT transport-receptor binding proteins can also be used to identify molecules that bind thereto, by contacting candidate test molecules under conditions conducive to binding, and detecting any binding that occurs.

4. DESCRIPTION OF THE FIGURES

Figur 1. Figure 1 shows the human PEPT1 predicted amino acid sequence determined from the sequence of the cDNA clone

coding for human PEPT1 (SEQ ID NO:176) (Liang R. *et al*. J. Biol. Chem. 270(12):6456-6463 (1995)), including the extracellular domain from amino acid 391 to 573 (Fei et al., Nature 368:563 (1994)).

Figures 2A-2C. Figures 2A-2C show the DNA sequence of the cDNA coding for the human intestinal peptide-associated transporter HPT1 and the corresponding putative amino acid sequence (bases 1 to 3345; Medline:94204643) (SEQ ID NOS: 177 and 178, respectively).

Figures 3A-3B. Figures 3A-3B show the putative Human Sucrase-isomaltase complex(hSI) amino acid sequence determined from the sequence of the cDNA clone coding for human sucrase-isomaltase complex (SEQ ID NO:179) (Chantret I., *et al*., Biochem. J. 285(Pt 3):915-923 (1992).

Figures 4A-4B. Figures 4A-4B show the D2H nucleotide and deduced amino acid sequence for the human D2H transporter (SEQ ID NOS:180 and 181, respectively) (Wells, R.G. *et al*.,J. Clin. Invest. 90:1959-1963 (1993).

Figures 5A-5C. Figure 5A is a schematic summary of the cloning of the DNA insert present in gene III of the phages selected from the phage display libraries into the expression vector pGex-4T-2. The gene insert in gene III of the phages was amplified by PCR using DNA primers which flank the gene insert and which contained recognition sequences for specific restriction endonucleases at their extreme 5′ sides. Alternatively, specific primers which amplify specific regions of the DNA inserts in gene III of the phages, and which contained recognition sequences for specific restriction endonucleases at their extreme 5′ sides, were used in PCR amplification experiments. Following amplification of the gene inserts, the amplified PCR fragments were digested with the restriction endonucleases Xho1 and Not1. Similarly the plasmid pGex-4T-2, which codes for the reporter protein glutathione S-transferase (GST), was digested with the restriction endonucleases Sal1 and Not1. The digested PCR fragments were ligated into the digested plasmid pGex-4T-2 using T4 DNA Ligase and the ligated

products were transformed into competent *Escherichia coli*, with selection of transformants on agar plates containing selection antibiotic. The selected clones were cultured, the plasmids were recovered and the in-frame sequence of the DNA insert in the plasmids was confirmed by DNA sequencing. The correct clones were subsequently used for expression of the GST-fusion proteins (SEQ ID NO:182); Figure 5B shows the series of full-length P31 (designated P31) (SEQ ID NO:43) and truncated peptides derived from P31 (clones # 101, 102, 103 and 119), (SEQ ID NOS:183, 184, 185, and 186, respectively) full-length PAX2 (designated PAX2) (SEQ ID NO:55) and truncated peptides derived from PAX2 (clones # 104, 105, 106) (SEQ ID NOS:170, 187, and 188, respectively) and full-length DCX8 (DCX8) (SEQ ID NO:23) and series of truncated peptides derived from DCX8 (clones # 107, 108, 109) (SEQ ID NOS:189, 190, and 191, respectively) that were expressed as fusion proteins to GST. The construction of these GST-fusion proteins is shown in Figure 5A. Figure 5C shows the series of full-length P31 (designated P31) (SEQ ID NO:43) and truncated peptides derived from P31 (clones # 103, 110, 119, 111, and 112) (SEQ ID NOS:185, 192, 193, 194, and 195, respectively), full-length PAX2 (designated PAX2) (SEQ ID NO:55) and truncated peptides derived from PAX2 (clones # 106, 113, 114, 115) (SEQ ID NOS:188, 196, 197, and 198, respectively) and full-length SNi10 (designated SNi10) (SEQ ID NO:4) and series of truncated peptides derived from SNi10 (clones # 116, 117, 118) (SEQ ID NOS:199, 200, and 201, respectively) that were expressed as fusion proteins to GST. The construction of these GST-fusion proteins is shown in Figure 5A. (Underlining and bold in Figs. 5A-5C are for orientation of the sequences.)

Figures 6A-6B. Figures 6A-6B show the binding of GST and GST-fusion proteins to recombinant hSI and to fixed C2BBe1 fixed cells as detected by ELISA assays. Figure 6A shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from SNi10 (designated GST-SNi10) and SNi34 (designated GST-SNi34) to

recombinant hSI. Figure 6B shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from SNi10 (designated GST-SNi10) and SNi34 (designated GST-SNi34) to fixed C2BBe1 cells.

Figures 7A-7M. Figures 7A-7M show the binding of GST peptide and truncated fusion proteins to fixed Caco-2 cells, fixed C2BBe1 cells, and fixed A431 cells or to recombinant GIT transport receptors D2H, HPT1, hPEPT1 or to BSA using increasing concentrations (expressed as μg/ml on the X-axis) of the control GST protein and the GST-fusion proteins, as detected by ELISA assays. Figure 7A shows the binding of the control protein GST, which does not contain a fusion peptide, and the series of GST-fusion proteins from P31 including the fusion to full-length P31 peptide (designated P31) (SEQ ID NO:43) and clone # 101 (designated P31,101), clone # 102 (designated P31, 102) and clone # 103 (designated P31,103). Figure 7B shows the binding of the control protein GST, which does not contain a fusion peptide, and the series of GST-fusion proteins from PAX2 including the fusion to full-length PAX2 peptide (designated PAX2) and clone # 104 (designated PAX2,104), clone # 105 (designated PAX2, 105) and clone # 106 (designated PAX2,106) (SEQ ID NOS:55, 170, 187, and 188, respectively). Figure 7C shows the binding of the control protein GST, which does not contain a fusion peptide, and the series of GST-fusion proteins from DCX8 including the fusion to full-length DCX8 peptide (designated DCX8) and clone # 107 (designated DCX8,107), clone # 108 (designated DCX8, 108) and clone # 109 (designated DCX8,109) (SEQ ID NOS:23, 189, 190, and 191, respectively). Figure 7D shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from DCX8 (designated GST-DCX8) and DCX11 (designated GST-DCX11) to recombinant D2H. Figure 7E shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from DCX8 (designated GST-DCX8) and DCX11 (designated GST-DCX11) to fixed C2BBe1 cells. Figure 7F shows the binding of the control protein GST, which does not contain a fusion

peptide, and the GST-fusion proteins from P31 (designated GST-P31) and 5PAX5 (designated GST-5PAX5) to recombinant hPEPT1. Figure 7G shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from P31 (designated GST-P31) and 5PAX5 (designated GST-5PAX5) to fixed C2BBe1 cells. Figure 7H shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from HAX42 (designated GST-HAX42) and PAX2 (designated GST-PAX2) to recombinant HPT1. Figure 7I shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from HAX42 (designated GST-HAX42) and PAX2 (designated GST-PAX2) to fixed C2BBe1 cells. Figure 7J shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from P31 (designated GST-P31) and truncated derivatives clone # 101 (designated GST-P31-101), clone # 102 (designated GST-P31-102), clone # 103 (designated GST-P31-103) to either recombinant hPEPT1 or to BSA. Figure 7K shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from P31 (designated GST-P31) and truncated derivatives clone # 101 (designated GST-P31-101), clone # 102 (designated GST-P31-102), clone # 103 (designated GST-P31-103) to either fixed C2BBe1 cells or to fixed A431 cells. Figure 7L shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from PAX2 (designated GST-PAX2) and truncated derivatives clone # 104 (designated GST-PAX2-104), clone # 105 (designated GST-PAX2-105), clone # 106 (designated GST-PAX2-106) to either recombinant hPEPT1 or to BSA. Figure 7M shows the binding of the control protein GST, which does not contain a fusion peptide, and the GST-fusion proteins from PAX2 (designated GST-PAX2) and truncated derivatives clone # 106 (designated GST-PAX2-106)to either fixed Caco-2 cells or to fixed A431 cells.

Figures 8A-8D. Figure 8 shows the transport of GST or GST-peptide fusion derivatives across polarized Caco-2 cells in

an apical to basolateral direction as a function of time (1-4 hours) as detected by ELISA assays. Figure 8A shows the transport of either GST, the GST fusion to full-length P31 peptide (designated P31) (SEQ ID NO:43) and the GST clone derivative clone # 103 (designated P31.103) across polarized Caco-2 cells in an apical to basolateral as a function of time (in hours) following initial administration of the proteins to the apical medium of polarized Caco-2 cells. The line designated No Protein corresponds to control assays in which buffer control was applied to the apical medium of polarized Caco-2 cells followed by sampling of the basolateral medium as a function of time (hours) and assay for GST by the ELISA assay. Figure 8B shows the transport of either GST, the GST fusion to full-length PAX2 peptide (designated PAX2) and the GST clone derivative clone # 106 (designated PAX2.106) across polarized Caco-2 cells in an apical to basolateral as a function of time (in hours) following initial administration of the proteins to the apical medium of polarized Caco-2 cells. The line designated No Protein corresponds to control assays in which buffer control was applied to the apical medium of polarized Caco-2 cells followed by sampling of the basolateral medium as a function of time (hours) and assay for GST by the ELISA assay. Figure 8C shows the transport of either GST, the GST fusion to full-length DCX8 peptide (designated DCX8), and the GST clone derivatives clone # 107 (designated DCX8.107) and clone # 109 (designated DCX8.109) across polarized Caco-2 cells in an apical to basolateral as a function of time (in hours) following initial administration of the proteins to the apical medium of polarized Caco-2 cells. The line designated No Protein corresponds to control assays in which buffer control was applied to the apical medium of polarized Caco-2 cells followed by sampling of the basolateral medium as a function of time (hours) and assay for GST by the ELISA assay. Figure 8D shows the amount of the GST and GST-fusion proteins (GST fusions to P31, P31-103, PAX2, PAX2.106, DCX8, DCX8-107, DCX8-109), used in the experiments shown in panels

A-C above, in the apical medium of the polarized Caco-2 cells as detected by ELISA assay.

Figures 9A-9B. Figures 9A-9B show the inhibition of GST-P31 binding to C2BBe1 fixed cells with varying concentration of competitors while holding the concentration of GST-P31 constant at 0.015 μM; the peptide competitors are ZElan024 which is the dansylated peptide version of P31 (SEQ ID NO:43) and ZElan044, ZElan049 and ZElan050 which are truncated, dansylated pieces of P31 (SEQ ID NO:43). Data is presented as O.D. versus peptide concentration (Figure 9A) and as percent inhibition of GST-P31 binding versus peptide concentration (Figure 9B).

Figures 10A-10C. Figures 10A-10C present a compilation of the results of competition ELISA studies of GST-P31, GST-PAX2, GST-SNi10 and GST-HAX42 versus listed dansylated peptides on fixed C2BBe1 cells ("Z" denotes ϵ-amino dansyl lysine). The pI of the dansylated peptides is also included. Estimated IC_{50} values are in μM and where present, IC_{50} ranges refer to results from multiple assays. If the IC_{50} value could not be determined, a ">" or "<" symbol is used. The GST/C2BBel column shows GST protein binding to fixed C2BBel cells.

Figures 11A-11B. Figure 11A shows the transport of GST or GST-peptide fusion derivatives across polarized Caco-2 cells in an apical to basolateral direction at 0, 0.5, 2 and 4 hours as detected by ELISA assays and described elsewhere in the text in full detail. The proteins used in the assay included GST, GST-P31 fusion, GST-5PAX5 fusion, GST-DCX8 fusion, GST-DCX11 fusion, GST-PAX2 fusion, GST-HAX42 fusion, GST-SNi34 fusion and GST-SNi10 fusion. The column designated No protein refers to control experiments in which buffer was applied to the apical medium of the cells and ELISA assay was performed on the corresponding basolateral medium of these cells at 0, 0.5, 2 and 4 hours post buffer addition. Figure 11B shows the internalization of GST or GST-peptide fusion derivatives within polarized Caco-2 cells following administration of the GST or GST-fusion protein derivatives

to the apical medium of polarized Caco-2 cells and subsequent recovery of the cells from the transwells and detection of the GST or GST fusions within the recovered cell lysates as detected by ELISA assays and as described elsewhere in the text in full detail. The proteins used in the assay included GST, GST-P31 fusion, GST-5PAX5 fusion, GST-DCX8 fusion, GST-DCX11 fusion, GST-PAX2 fusion, GST-HAX42 fusion, GST-SNi34 fusion and GST-SNi10 fusion. The column designated No protein refers to control experiments in which buffer was applied to the apical medium of the cells and ELISA assay was performed on the corresponding cell lysates of these cells at the end of the experiment.

Figure 12. Figure 12 shows the binding of GST and GST-fusion proteins to fixed Caco-2 cells, and the corresponding proteins following digestion with the protease Thrombin which cleaves at a recognition site between the GST portion and the fused peptide portion of the GST-fusion protein. The symbol "-" refers to proteins which were not digested with thrombin and the symbol "+" refers to proteins which were digested with thrombin prior to use in the binding assay. The binding of the proteins to the fixed Caco-2 cells was detected by ELISA assays.

Figures 13A-13B. Figures 13A-13B show binding of peptide-coated nanoparticles to fixed Caco-2 cells.

Figures 14A-14B. Figures 14A-14B show the binding of (A) dansylated peptide SNi10 to the purified hSI receptor and BSA and (B) dansylated peptides and peptide-loaded insulin-containing PLGA particles to fixed C2BBel cells. Figure 14B depicts binding of dansylated peptides corresponding to P31 (SEQ ID NO:43), PAX2, HAX42, and SNi10 to fixed C2BBel cells, as well as the insulin-containing PLGA particles adsorbed with each of these peptides. Data is presented with background subtracted.

Figures 15A-15B. Figure 15 shows the binding of peptide-coated particles to A) S100 and B) P100 fractions harvested from Caco-2 cells. The dilution series 1:2 - 1:64 represents particle concentrations in the range 0.0325-0.5 μg/well.

Data is presented with background subtracted. The particles are identified as follows: 939, no peptide; 1635, scrambled PAX2; 1726, P31 D-Arg 16-mer (ZElan053); 1756, HAX42; 1757, PAX2; 1758, HAX42/PAX2.

Figures 16A-16B. Figure 16 shows the binding of dansylated peptides to P100 fractions harvested from Caco-2 cells. Peptides were assayed in the range 0.0032-2.5 μg/well. Data is presented with background subtracted. A) HAX42, P31 D-form (ZElan 053) and scrambled PAX2; B) PAX2, HAX42 and scrambled PAX2.

Figures 17A-17B. Figures 17A and 17B show (A) the systemic blood glucose and (B)insulin levels following intestinal administration of control (PBS); insulin solution; insulin particles; all 8 peptides mix particles and study group peptide-particles according to this invention (100iu insulin loading).

Figures 18A-18B. Figures 18A and 18B show the (A) systemic blood glucose and (B)insulin levels following intestinal administration of control (PBS); insulin solution; insulin particles and study group peptide-particles according to this invention (300iu insulin loading).

Figure 19. Figure 19 shows the enhanced plasma levels of leuprolide upon administration of P31 (SEQ ID NO:43) and PAX2 coated nanoparticles loaded with leuprolide relative to subcutaneous injection. Group 1 was administered leuprolide acetate (12.5 μg) subcutaneously. Group 2 was administered intraduodenally uncoated leuprolide acetate particles (600 μg, 1.5 ml). Group 3 was intraduodenally administered leuprolide acetate particles coated with PAX2 (600 μg; 1.5 ml). Group 4 was administered intraduodenally leuprolide acetate particles coated with P31 (SEQ ID NO:43) (600 μg, 1.5 ml).

Figure 20. Figure 20 lists P31 (SEQ ID NO:43) known protein homologies.

Figures 21A-21C. Figures 21A-21C list DCX8 known protein homologies.

Figure 22. Figure 22 lists DAB10 known protein homologies.

Figure 23. Figure 23 shows the DNA sequence (SEQ ID NO:211) and the corresponding amino acid sequence (SEQ ID NO:212) for glutathione S-transferase (Smith and Johnson, 1988, Gene 7:31-40).

5. DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to proteins (*e.g.*, peptides) that bind to GIT transport receptors and nucleic acids that encode such proteins. The invention further relates to fragments and other derivatives of such proteins. Nucleic acids encoding such fragments or derivatives are also within the scope of the invention. The invention further relates to fragments (and derivatives and analogs thereof) of GIT transport receptor-binding peptides which comprise one or more domains of the GIT transport receptor-binding peptides.

The invention also relates to derivatives of GIT transport receptor-binding proteins and analogs of the invention which are functionally active, *i.e.*, they are capable of displaying one or more known functional activities associated with a full-length GIT transport receptor-binding peptide. Such functional activities include but are not limited to ability to bind to a GIT transport receptor, antigenicity [ability to bind (or compete with peptides for binding) to an anti-GIT transport receptor-binding peptide antibody], immunogenicity (ability to generate antibody which binds to GIT transport receptor-binding peptide), etc.

Production of the foregoing proteins and derivatives, by, *e.g.*, recombinant methods, is also provided.

Antibodies to GIT transport receptor-binding proteins, derivatives and analogs, are additionally provided.

The present invention also relates to therapeutic and diagnostic methods and compositions based on GIT transport receptor-binding proteins and nucleic acids.

The invention is illustrated by way of examples *infra*.

For clarity of disclosure, and not by way of limitation, the detailed description of the invention is divided into the subsections which follow.

5.1. GIT Transport Receptor-Binding Peptides, Derivatives and Analogs

The invention relates to peptides that bind GIT transport receptors and derivatives (including but not limited to fragments) and analogs thereof. In specific embodiments, of the present invention, such peptides that bind to GIT transport receptor include but are not limited to those containing as primary amino acid sequences, all or part of the amino acid sequences substantially as depicted in Table 7 (SEQ ID NOS:1-55). Nucleic acids encoding such peptides, derivatives and peptide analogs are also provided. In one embodiment, the GIT transport receptor-binding peptides are encoded by the nucleic acids having the nucleotide sequences set forth in Table 8 *infra* (SEQ ID NOS:56-109). Proteins whose amino acid sequence comprise, or alternatively, consist of SEQ ID NOS:1-55 or a portion thereof that mediates binding to a GIT transport receptor are provided.

The production and use of derivatives and analogs related to GIT transport receptor-binding peptides are within the scope of the present invention. In a specific embodiment, the derivative or analog is functionally active, *i.e.*, capable of exhibiting one or more functional activities associated with a full-length GIT transport receptor-binding peptide. For example, such derivatives or analogs which have the desired immunogenicity or antigenicity can be used, in immunoassays, for immunization, etc. A specific embodiment relates to a GIT transport receptor-binding peptide fragment that can be bound by an anti-GIT transport receptor-binding peptide antibody. In a preferred aspect, the derivatives or analogs have the ability to bind to a GIT transport receptor. Derivatives or analogs of GIT transport receptor-binding peptides can be tested for the desired activity by procedures

known in the art, including binding to a GIT transport receptor domain or to Caco-2 cells, *in vitro*, or to intestinal tissue, *in vivo*. (See the Examples *infra*.)

In particular, derivatives can be made by altering GIT transport receptor-binding peptide sequences by substitutions, additions or deletions that provide for functionally equivalent molecules. Due to the degeneracy of nucleotide coding sequences, other nucleotide sequences which encode substantially the same amino acid sequence may be used in the practice of the present invention. These include but are not limited to nucleotide sequences which are altered by the substitution of different codons that encode a functionally equivalent amino acid residue within the sequence, thus producing a silent change. Likewise, the GIT transport receptor-binding peptide derivatives of the invention include, but are not limited to, those containing, as a primary amino acid sequence, all or part of the amino acid sequence of a GIT transport receptor-binding peptide including altered sequences in which functionally equivalent amino acid residues are substituted for residues within the sequence resulting in a silent change. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity which acts as a functional equivalent, resulting in a silent alteration. Substitutes for an amino acid within the sequence may be selected from other members of the class to which the amino acid belongs. For example, the nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine. The positively charged (basic) amino acids include arginine, lysine and histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

In a specific embodiment of the invention, proteins consisting of or, alternatively, comprising all or a fragment

of a GIT transport receptor-binding peptide consisting of at least 5, 10, 15, 20, 25, 30 or 35 (contiguous) amino acids of the full-length GIT transport receptor-binding peptide are provided. In a specific embodiment, such proteins are not more than 20, 30, 40, 50, or 75 amino acids in length. Derivatives or analogs of GIT transport receptor-binding peptides include but are not limited to those molecules comprising regions that are substantially homologous to GIT transport receptor-binding peptides or fragments thereof (*e.g.*, at least 50%, 60%, 70%, 80% or 90% identity) (*e.g.*, over an identical size sequence or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art) or whose encoding nucleic acid is capable of hybridizing to a coding GIT transport receptor-binding peptide sequence, under stringent, moderately stringent, or nonstringent conditions.

In a specific embodiment, the GIT transport receptor-binding derivatives of the invention are not known proteins with homology to the GIT transport receptor-binding peptides of the invention or portions thereof.

The GIT transport receptor-binding peptide derivatives and analogs of the invention can be produced by various methods known in the art. The manipulations which result in their production can occur at the gene or protein level. For example, the cloned GIT transport receptor-binding peptide gene sequence can be modified by any of numerous strategies known in the art (Maniatis, T., 1990, Molecular Cloning, A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York). The sequence can be cleaved at appropriate sites with restriction endonuclease(s), followed by further enzymatic modification if desired, isolated, and ligated *in vitro*. In the production of the gene encoding a derivative or analog of GIT transport receptor-binding peptides, care should be taken to ensure that the modified gene remains within the same translational reading frame uninterrupted by translational

stop signals, in the gene region where the desired GIT transport receptor-binding peptides activity is encoded.

Additionally, nucleic acid sequences encoding the GIT transport receptor-binding peptides can be mutated *in vitro* or *in vivo*, to create and/or destroy translation, initiation, and/or termination sequences, or to create variations in coding regions and/or form new restriction endonuclease sites or destroy preexisting ones, to facilitate further *in vitro* modification. Any technique for mutagenesis known in the art can be used, including but not limited to, chemical mutagenesis, *in vitro* site-directed mutagenesis (Hutchinson, C., et al., 1978, J. Biol. Chem 253:6551), use of TAB® linkers (Pharmacia), use of PCR primers containing mutation(s) for use in amplification, etc.

Manipulations of GIT transport receptor-binding peptide sequences may also be made at the protein level. Included within the scope of the invention are GIT transport receptor-binding peptide fragments or other derivatives or analogs which are differentially modified during or after translation or chemical synthesis, *e.g.*, by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, $NaBH_4$; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc. In a specific embodiment, the amino- and/or carboxy-termini are modified.

In addition, GIT transport receptor-binding peptides and analogs and derivatives thereof can be chemically synthesized. For example, a peptide corresponding to all or a portion of a GIT transport receptor-binding peptide which comprises the desired domain or which mediates the desired activity *in vitro*, can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical

amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the GIT transport receptor-binding peptide sequence. Non-classical amino acids include but are not limited to the D-isomers of the common amino acids, α-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ-Abu, ϵ-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β-alanine, fluoro-amino acids, designer amino acids such as β-methyl amino acids, Cα-methyl amino acids, Nα-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

In a specific embodiment, the GIT transport receptor-binding peptide derivative is a chimeric, or fusion, peptide comprising a GIT transport receptor-binding peptide or fragment thereof (preferably consisting of at least a domain or motif of the GIT transport receptor-binding peptide, or at least 6, 10, 15, 20, 25, 30 or all amino acids of the GIT transport receptor-binding peptides or a binding portion thereof) joined at its amino- or carboxy-terminus via a peptide bond to an amino acid sequence of a different peptide. In one embodiment, such a chimeric peptide is produced by recombinant expression of a nucleic acid encoding the protein (comprising a transport receptor-coding sequence joined in-frame to a coding sequence for a different protein). Such a chimeric product can be made by ligating the appropriate nucleic acid sequences encoding the desired amino acid sequences to each other by methods known in the art, in the proper coding frame, and expressing the chimeric product by methods commonly known in the art. Alternatively, such a chimeric product may be made by protein synthetic techniques, *e.g.*, by use of a peptide synthesizer. Chimeric genes comprising portions of GIT transport receptor fused to any heterologous protein-encoding sequences may be constructed. A specific embodiment relates to a chimeric

protein comprising a fragment of GIT transport receptor-binding peptides of at least six amino acids.

In another specific embodiment, the GIT transport receptor-binding peptide derivative is a molecule comprising a region of homology with a GIT transport receptor-binding peptide. By way of example, in various embodiments, a first protein region can be considered "homologous" to a second protein region when the amino acid sequence of the first region is at least 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, or 95% identical, when compared to any sequence in the second region of an equal number of amino acids as the number contained in the first region or when compared to an aligned sequence of the second region that has been aligned by a computer homology program known in the art. For example, a molecule can comprise one or more regions homologous to a GIT transport receptor-binding peptide domain (see *infra*) or a portion thereof.

The GIT transport receptor-binding proteins and derivatives thereof of the invention can be assayed for binding activity by suitable *in vivo* or *in vitro* assays, *e.g.*, as described in the examples *infra* and/or as will be known to the skilled artisan.

Other specific embodiments of derivatives and analogs are described in the subsection below and examples sections *infra*.

5.2. Motifs/Derivatives of GIT Transport Receptor-Binding Peptides Containing <u>One or More Domains of The Protein</u>

In a specific embodiment, the invention relates to GIT transport receptor-binding peptide derivatives and analogs, in particular GIT transport receptor-binding peptide fragments and derivatives of such fragments, that comprise, or alternatively consist of, one or more domains of a GIT transport receptor-binding peptide. In particular, examples of such domains are identified in the examples *infra*.

5.3. Synthesis of Peptides

The peptides and derivatives of the present invention may be chemically synthesized or synthesized using recombinant DNA techniques.

5.3.1. Procedure For Solid Phase Synthesis

Peptides may be prepared chemically by methods that are known in the art. For example, in brief, solid phase peptide synthesis consists of coupling the carboxyl group of the C-terminal amino acid to a resin and successively adding N-alpha protected amino acids. The protecting groups may be any known in the art. Before each new amino acid is added to the growing chain, the protecting group of the previous amino acid added to the chain is removed. The coupling of amino acids to appropriate resins is described by Rivier et al., U.S. Patent No. 4,244,946. Such solid phase syntheses have been described, for example, by Merrifield, 1964, J. Am. Chem. Soc. 85:2149; Vale et al., 1981, Science 213:1394-1397; Marki et al., 1981, J. Am. Chem. Soc. 103:3178 and in U.S. Patent Nos. 4,305,872 and 4,316,891. In a preferred aspect, an automated peptide synthesizer is employed.

By way of example but not limitation, peptides can be synthesized on an Applied Biosystems Inc. ("ABI") model 431A automated peptide synthesizer using the "Fastmoc" synthesis protocol supplied by ABI, which uses 2-(1H-Benzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate ("HBTU") (R. Knorr et al., 1989, Tet. Lett., 30:1927) as coupling agent. Syntheses can be carried out on 0.25 mmol of commercially available 4-(2',4'-dimethoxyphenyl-(9-fluorenyl-methoxycarbonyl)-aminomethyl)-phenoxy polystyrene resin ("Rink resin" from Advanced ChemTech) (H. Rink, 1987, Tet. Lett. 28:3787). Fmoc amino acids (1 mmol) are coupled according to the Fastmoc protocol. The following side chain protected Fmoc amino acid derivatives are used: FmocArg(Pmc)OH; FmocAsn(Mbh)OH; FmocAsp(^{t}Bu)OH; FmocCys(Acm)OH; FmocGlu(^{t}Bu)OH; FmocGln(Mbh)OH; FmocHis(Tr)OH;

FmocLys(Boc)OH; FmocSer(^{t}Bu)OH; FmocThr(^{t}Bu)OH; FmocTyr(^{t}Bu)OH. [Abbreviations: Acm, acetamidomethyl; Boc, tert-butoxycarbonyl; ^{t}Bu, tert-butyl; Fmoc, 9-fluorenylmethoxycarbonyl; Mbh, 4,4'-dimethoxybenzhydryl; Pmc, 2,2,5,7,8-pentamethylchroman-6-sulfonyl; Tr, trityl].

Synthesis is carried out using N-methylpyrrolidone (NMP) as solvent, with HBTU dissolved in N,N-dimethylformamide (DMF). Deprotection of the Fmoc group is effected using approximately 20% piperidine in NMP. At the end of each synthesis the amount of peptide present is assayed by ultraviolet spectroscopy. A sample of dry peptide resin (about 3-10 mg) is weighed, then 20% piperidine in DMA (10 ml) is added. After 30 min sonication, the UV (ultraviolet) absorbance of the dibenzofulvene-piperidine adduct (formed by cleavage of the N-terminal Fmoc group) is recorded at 301 nm. Peptide substitution (in mmol g^{-1}) can be calculated according to the equation:

$$\text{substitution} = \frac{A \times v}{7800 \times w} \times 1000$$

where A is the absorbance at 301 nm, v is the volume of 20% piperidine in DMA (in ml), 7800 is the extinction coefficient (in mol^{-1}dm^{3}cm^{-1}) of the dibenzofulvene-piperidine adduct, and w is the weight of the peptide-resin sample (in mg).

Finally, the N-terminal Fmoc group is cleaved using 20% piperidine in DMA, then acetylated using acetic anhydride and pyridine in DMA. The peptide resin is thoroughly washed with DMA, CH_2Cl_2 and finally diethyl ether.

5.3.2. <u>Cleavage And Deprotection</u>

By way of example but not limitation, cleavage and deprotection can be carried out as follows: The air-dried peptide resin is treated with ethylmethyl-sulfide (EtSMe), ethanedithiol (EDT), and thioanisole (PhSMe) for approximately 20 min. prior to addition of 95% aqueous trifluoracetic acid (TFA). A total volume of approximately 50 ml of these reagents per gram of peptide-resin is used.

The following ratio is used: TFA:EtSMe:EDT:PhSMe (10:0.5:0.5:0.5). The mixture is stirred for 3 h at room temperature under an atmosphere of N_2. The mixture is filtered and the resin washed with TFA (2 x 3 ml). The combined filtrate is evaporated *in vacuo*, and anhydrous diethyl ether added to the yellow/orange residue. The resulting white precipitate is isolated by filtration. See King et al., 1990, Int. J. Peptide Protein Res. 36:255-266 regarding various cleavage methods.

5.3.3. Purification of the Peptides

Purification of the synthesized peptides can be carried out by standard methods including chromatography (*e.g.*, ion exchange, affinity, and sizing column chromatography, high performance liquid chromatography (HPLC)), centrifugation, differential solubility, or by any other standard technique.

5.3.4. Biological Peptide Libraries

Biological peptide libraries can be used to express and identify peptides that bind to GIT transport receptors. According to this second approach, involving recombinant DNA techniques, peptides can, by way of example, be expressed in biological systems as either soluble fusion proteins or viral capsid proteins.

5.3.4.1. Methods To Identify Binders: Construction Of Libraries

In a specific embodiment, the peptides of the invention that specifically bind to GIT transport receptors are identified by screening a random peptide library by contacting the library with a ligand selected from among HPT1, hPEPT1, D2H, or hSI (or a molecule consisting essentially of an extracellular domain thereof or fragment of the domain) to identify members of the library that specifically bind to the ligand.

In a particular embodiment, a process to identify the peptides of the present method utilizes a library of recombinant vectors constructed by methods well known in the art and comprises screening a library of recombinant vectors expressing inserted synthetic oligonucleotide sequences encoding extracellular GIT transport receptor domains, for example, attached to an accessible surface structural protein of a vector to isolate those members producing peptides that bind to HPT1, hPEPT1, D2H, or hSI. The nucleic acid sequence of the inserted synthetic oligonucleotides of the isolated vector is determined and the amino acid sequence encoded can be deduced to identify a binding domain that binds the ligand of choice (*e.g.*, HPT1, hPEPT1, D2H, or hSI).

The present invention encompasses a method for identifying a peptide which binds to a ligand selected from among HPT1, hPEPT1, D2H, or hSI comprising: screening a library of random peptides with the ligand (or an extracellular domain or fragment thereof) under conditions conducive to ligand binding and isolating the peptide which binds to the ligand. Additionally, the methods of the invention further comprise determining the nucleotide sequence encoding the binding domain of the peptide identified to deduce the amino acid sequence of the binding domain.

5.3.4.2. Preparation of Extracellular Domain Ligand

In a specific embodiment, molecules consisting essentially of an extracellular domain of the desired GIT transport receptor or a fragment of an extracellular domain are used to screen a random peptide library for binding thereto. Preferably, a nucleic acid encoding the extracellular domain is cloned and recombinantly expressed, and the domain is then purified for use. The GIT transport receptor is preferably selected from among HPT1, hPEPT1, D2H, or hSI.

5.3.4.3. Methods to Identify Binders: Screening Libraries

Once a suitable random peptide library has been constructed (or otherwise obtained), the library is screened to identify peptides having binding affinity for the GIT transport receptor, *e.g.*, HPT1, hPEPT1, D2H, or hSI. In a preferred aspect, the library is a TSAR library (see U.S. Patent No. 5,498,538 dated March 12, 1996 and PCT Publication WO 94/18318 dated August 18, 1994, both of which are incorporated by reference herein in their entireties). Screening the libraries can be accomplished by any of a variety of methods known to those of skill in the art. See, *e.g.*, the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, Adv. Exp. Med. Biol. 251: 215-218; Scott and Smith, 1990, Science 249: 386-390; Fowlkes et al., 1992; BioTechniques 13: 422-427; Oldenburg et al., 1992, Proc. Natl. Acad. Sci. USA 89: 5393-5397; Yu et al., 1994, Cell 76: 933-945; Staudt et al., 1988, Science 241: 577-580; Bock et al., 1992, Nature 355: 564-566; Tuerk et al., 1992, Proc. Natl. Acad. Sci. USA 89: 6988-6992; Ellington et al., 1992, Nature 355: 850-852; U.S. Patent No. 5,096,815, U.S. Patent No. 5,223,409, and U.S. Patent No. 5,198,346, all to Ladner et al.; and Rebar and Pabo, 1993, Science 263: 671-673. See also PCT publication WO 94/18318, dated August 18, 1994.

One of ordinary skill in the art will recognize that, with suitable modifications, the screening methods described below would be suitable for a wide variety of biological expression libraries.

Once a library has been constructed or otherwise obtained, the library is screened to identify binding molecules having specific binding affinity for a ligand for a GIT transport receptor preferably selected from among HPT1, hPEPT1, D2H, or hSI.

Screening the libraries can be accomplished by any of a variety of methods known to those of skill in the art. Exemplary screening methods are described in Fowlkes et al.,

1992, BioTechniques, 13:422-427 and include contacting the vectors with an immobilized target ligand and harvesting those vectors that bind to said ligand. Such useful screening methods, are designated "panning" methods. In panning methods useful to screen the present libraries, the target ligand can be immobilized on plates, beads (such as magnetic beads), sepharose, beads used in columns, etc. If desired, the immobilized target ligand can be "tagged", *e.g.*, using labels such as biotin, fluoroscein isothiocyanate, rhodamine, etc. *e.g.* for FACS sorting. Panning is also disclosed in Parmley, S.F. and Smith, G.P., 1988, Gene 73: 305-318.

In a particular embodiment of the invention, the library can be screened with a recombinant receptor domain. In another embodiment, the library can be screened successively with receptor domains and then on CaCO-2 cells.

For screening of the peptide libraries *in vitro*, the solvent requirements involved in screening are not limited to aqueous solvents; thus, nonphysiological binding interactions and conditions different from those found *in vivo* can be exploited.

Screening a library can be achieved using a method comprising a first "enrichment" step and a second filter lift as follows. The following description is given by way of example, not limitation.

Binders from an expressed library (*e.g.*, in phage) capable of binding to a given ligand ("positives") are initially enriched by one or two cycles of panning or affinity chromatography. A microtiter well is passively coated with the ligand (*e.g.*, about 10 μg in 100 μl). The well is then blocked with a solution of BSA to prevent non-specific adherence of the phage of the library to the plastic surface. For example, about 10^{11} phage particles expressing peptides are then added to the well and incubated for several hours. Unbound phage are removed by repeated washing of the plate, and specifically bound phage are eluted using an acidic glycine-HCl solution or other elution buffer. The

eluted phage solution is neutralized with alkali, and amplified, *e.g.*, by infection of *E. coli* and plating on large petri dishes containing Luria broth (LB) in agar. Amplified cultures expressing the binding peptides are then titered and the process repeated. Alternatively, the ligand can be covalently coupled to agarose or acrylamide beads using commercially available activated bead reagents. The phage solution is then simply passed over a small column containing the coupled bead matrix which is then washed extensively and eluted with acid or other eluant. In either case, the goal is to enrich the positives to a frequency of about > $1/10^5$.

Following enrichment, a filter lift assay is conducted. For example, when specific binders are expressed in phage, approximately 1-2 x 10^5 phage are added to 500 μl of log phase *E. coli* and plated on a large Luria Broth-agarose plate with 0.7% agarose in broth. The agarose is allowed to solidify, and a nitrocellulose filter (*e.g.*, 0.45 μ) is placed on the agarose surface. A series of registration marks is made with a sterile needle to allow re-alignment of the filter and plate following development as described below. Phage plaques are allowed to develop by overnight incubation at 37 °C (the presence of the filter does not inhibit this process). The filter is then removed from the plate with phage from each individual plaque adhered *in situ*. The filter is then exposed to a solution of BSA or other blocking agent for 1-2 hours to prevent non-specific binding of the ligand (or "probe").

The probe itself is labeled, for example, either by biotinylation (using commercial NHS-biotin) or direct enzyme labeling, *e.g.*, with horse radish peroxidase or alkaline phosphatase. Probes labeled in this manner are indefinitely stable and can be re-used several times. The blocked filter is exposed to a solution of probe for several hours to allow the probe to bind *in situ* to any phage on the filter displaying a peptide with significant affinity to the probe. The filter is then washed to remove unbound probe, and then developed by exposure to enzyme substrate solution (in the

case of directly labeled probe) or further exposed to a solution of enzyme-labeled avidin (in the case of biotinylated probe). Positive phage plaques are identified by localized deposition of colored enzymatic cleavage product on the filter which corresponds to plaques on the original plate. The developed filter is simply realigned with the plate using the registration marks, and the "positive" plaques are cored from the agarose to recover the phage. Because of the high density of plaques on the original plate, it may be difficult to isolate a single plaque from the plate on the first pass. Accordingly, phage recovered from the initial core can be re-plated at low density and the process can be repeated to allow isolation of individual plaques and hence single clones of phage.

Successful screening experiments are optimally conducted using 3 rounds of serial screening. The recovered cells are then plated at a low density to yield isolated colonies for individual analysis. The individual colonies are selected and used to inoculate LB culture medium containing ampicillin. After overnight culture at 37°C, the cultures are then spun down by centrifugation. Individual cell aliquots are then retested for binding to the target ligand attached to the beads. Binding to other beads having attached thereto a non-relevant ligand, can be used as a negative control.

One aspect of screening the libraries is that of elution. The following discussion is applicable to any system where the random peptide is expressed on a surface fusion molecule. It is conceivable that the conditions that disrupt the peptide-target interactions during recovery of the phage are specific for every given peptide sequence from a plurality of proteins expressed on phage. For example, certain interactions may be disrupted by acid pH but not by basic pH, and *vice versa*. Thus, it may be desirable to test a variety of elution conditions (including but not limited to pH 2-3, pH 12-13, excess target in competition, detergents, mild protein denaturants, urea, varying temperature, light,

presence or absence of metal ions, chelators, etc.) and compare the primary structures of the binding proteins expressed on the phage recovered for each set of conditions to determine the appropriate elution conditions for each ligand/binding protein combination. Some of these elution conditions may be incompatible with phage infection because they are bactericidal and will need to be removed by dialysis (*i.e.*, dialysis bag, Centricon/Amicon microconcentrators).

In a preferred embodiment, a phage display library of random peptides is screened to select phage expressing peptides that bind to a GIT transport receptor. Preferably, a first step is to isolate a preselected phage library. The "preselected phage library" is a library consisting of a subpopulation of a phage display library. This subpopulation can be formed by initially screening against either a target GIT transport receptor (or domain thereof) so as to permit the selection of a subpopulation of phages which specifically bind to the receptor. Alternatively, the subpopulation can be formed by screening against a target cell or cell type or tissue type or tissue barrier of the gastro-intestinal tract, so as to permit the selection of a subpopulation of phages which either bind specifically to the target cell or target cell type or target tissue or target tissue barrier, or which binds to and/or is transported across (or between) the target cell or target cell type or target tissue or target tissue barrier either *in situ* or *in vivo*. This preselected phage library or subpopulation of selected phages can also be rescreened against the target GIT transport receptor, permitting the further selection of a subpopulation of phages which bind to the GIT transport receptor or target cell or target cell type or target tissue or target tissue barrier or which bind to and/or is transported across the target cell, target tissue or target tissue barrier either *in situ* or *in vivo*. Such rescreening can be repeated from zero to 30 times with each successive "pre-selected phage library" generating additional pre-selected phage libraries.

In a preferred embodiment, a preselected phage library binding a ligand that is a GIT transport receptor preferably selected from among HPT1, hPEPT1, D2H, or hSI is obtained by an *in vitro* screening step as described above, and then the phage are optionally further characterized using *in vitro* assays consisting of binding phage directly to the receptor domain of interest or, alternatively, to Caco-2 cells or using *in vivo* assays. In another preferred embodiment, *in vivo* assays are used that measure uptake of phage by intestinal tissue or, alternatively, through the GIT. In alternative embodiments, such further *in vitro* or *in vivo* assays can be used as the initial screening step.

In vivo assays that may be used are described in the examples *infra*.

5.4. Generation of Antibodies to GIT Transport Receptor-Binding Peptides and Derivatives Thereof

According to the invention, a GIT transport receptor-binding peptide, fragments or other derivatives, or analogs thereof, may be used as an immunogen to generate antibodies which immunospecifically bind such an immunogen. Such antibodies include but are not limited to polyclonal, monoclonal, chimeric, single chain, Fab fragments, and an Fab expression library.

Various procedures known in the art may be used for the production of polyclonal antibodies to a GIT transport receptor-binding peptide or derivative or analog. For the production of antibody, various host animals can be immunized by injection with the native GIT transport receptor-binding peptides, or a synthetic version, or derivative (*e.g.*, fragment) thereof, including but not limited to rabbits, mice, rats, fowl, etc. Various adjuvants may be used to increase the immunological response, depending on the host species, including but not limited to Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet

hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum.

For preparation of monoclonal antibodies directed toward a GIT transport receptor-binding peptide or analog thereof, any technique which provides for the production of antibody molecules by continuous cell lines in culture may be used. For example, the hybridoma technique originally developed by Kohler and Milstein (1975, Nature 256:495-497), as well as the trioma technique, the human B-cell hybridoma technique (Kozbor et al., 1983, Immunology Today 4:72), and the EBV-hybridoma technique to produce human monoclonal antibodies (Cole et al., 1985, in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc., pp. 77-96). In an additional embodiment of the invention, monoclonal antibodies can be produced in germ-free animals utilizing recent technology (PCT/US90/02545). According to the invention, human antibodies may be used and can be obtained by using human hybridomas (Cote et al., 1983, Proc. Natl. Acad. Sci. U.S.A. 80:2026-2030) or by transforming human B cells with EBV virus *in vitro* (Cole et al., 1985, in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, pp. 77-96). According to the invention, techniques developed for the production of "chimeric antibodies" (Morrison et al., 1984, Proc. Natl. Acad. Sci. U.S.A. 81:6851-6855; Neuberger et al., 1984, Nature 312:604-608; Takeda et al., 1985, Nature 314:452-454) by splicing the genes from a mouse antibody molecule specific for GIT transport receptor-binding peptides together with genes from a human antibody molecule of appropriate biological activity can be used.

According to the invention, techniques described for the production of single chain antibodies (U.S. Patent 4,946,778) can be adapted to produce GIT transport receptor-binding peptide-specific single chain antibodies. An additional embodiment of the invention utilizes the techniques described for the construction of Fab expression libraries (Huse et al., 1989, Science 246:1275-1281) to allow

rapid and easy identification of monoclonal Fab fragments with the desired specificity for GIT transport receptor-binding peptides, derivatives, or analogs.

Antibody fragments which contain the idiotype of the molecule can be generated by known techniques. For example, such fragments include but are not limited to: the $F(ab')_2$ fragment which can be produced by pepsin digestion of the antibody molecule; the Fab' fragments which can be generated by reducing the disulfide bridges of the $F(ab')_2$ fragment, the Fab fragments which can be generated by treating the antibody molecule with papain and a reducing agent, and Fv fragments.

In the production of antibodies, screening for the desired antibody can be accomplished by techniques known in the art, *e.g.* ELISA (enzyme-linked immunosorbent assay). For example, to select antibodies which recognize a specific domain of a GIT transport receptor-binding peptide, one may assay generated hybridomas for a product which binds to a GIT transport receptor-binding peptide fragment containing such a domain.

Antibodies specific to a domain of a GIT transport receptor-binding peptide are also provided.

The foregoing antibodies can be used in methods known in the art relating to the localization and activity of the GIT transport receptor-binding peptide sequences of the invention, *e.g.*, for imaging these peptides after *in vivo* administration (*e.g.*, to monitor treatment efficacy), measuring levels thereof in appropriate physiological samples, in diagnostic methods, etc. For instance, antibodies or antibody fragments specific to a domain of a GIT transport receptor-binding peptide or to a derivative of a peptide, such as a dansyl group or some other epitope introduced into the peptide, can be used to 1) identify the presence of the peptide on a nanoparticle or other substrate; 2) quantify the amount of peptide on the nanoparticle; 3)measure the level of the peptide in appropriate physiological samples; 4) perform immunohistology on tissue

samples; 5) image the peptide after *in vivo* administration; 6) purify the peptide from a mixture using an immunoaffinity column or 7) bind or fix the peptide to the surface of nanoparticle. This last use envisions attaching the antibody (or fragment of the antibody) to the surface of drug-loaded nanoparticles or other substrate and then incubating this conjugate with the peptide. This procedure results in binding of the peptide in a certain fixed orientation, resulting in a particle that contains the peptide bound to the antibody in such a way that the peptide is fully active.

Abtides (or Antigen binding peptides) specific to a domain of a GIT transport receptor-binding peptide or to a derivative of a peptide, such as a dansyl group or some other epitope introduced into the peptide, can be used for the same seven purposes identified above for antibodies.

5.5. Assays of GIT Transport Receptor-Binding Peptides, Derivatives and Analogs

The functional activity of GIT transport receptor-binding peptides, derivatives and analogs can be assayed by various methods.

In a preferred embodiment, in which binding to a GIT transport receptor is being assayed, the binding can be assayed by *in vivo* or *in vitro* assays such as described in the examples *infra*, or by other means that are known in the art.

In another embodiment, where one is assaying for the ability to bind or compete with full-length GIT transport receptor-binding peptide for binding to anti-GIT transport receptor-binding peptide antibody, various immunoassays known in the art can be used, including but not limited to competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitin reactions, immunodiffusion assays, *in situ* immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western

blots, precipitation reactions, agglutination assays (*e.g.*, gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labelled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

Other methods will be known to the skilled artisan and are within the scope of the invention.

5.6. <u>Uses</u>

The invention provides compositions comprising the GIT transport receptor-binding proteins of the invention bound to a material comprising an active agent. Such compositions have use in targeting the active agent to the GIT and/or in facilitating transfer through the lumen of the GIT into the systemic circulation. Where the active agent is an imaging agent, such compositions can be administered *in vivo* to image the GIT (or particular transport receptors thereof). Other active agents include but are not limited to: any drug or antigen or any drug- or antigen-loaded or drug- or antigen-encapsulated nanoparticle, microparticle, liposome, or micellar formulation capable of eliciting a biological response in a human or animal. Examples of drug- or antigen-loaded or drug- or antigen-encapsulated formulations include those in which the active agent is encapsulated or loaded into nano- or microparticles, such as biodegradable nano- or microparticles, and which have the GIT transport receptor-binding protein or derivative or analog adsorbed, coated or covalently bound, such as directly linked or linked via a linking moiety, onto the surface of the nano- or microparticle. Additionally, the protein, derivative or

analog can form the nano- or microparticle itself or the protein, derivative or analog can be covalently attached to the polymer or polymers used in the production of the biodegradable nano- or microparticles or drug-loaded or drug-encapsulated nano- or microparticles or the peptide can be directly conjugated to the active agent. Such conjugations to active agents include fusion proteins in which a DNA sequence coding for the peptide is fused in-frame to the gene or cDNA coding for a therapeutic peptide or protein such that the modified gene codes for a recombinant fusion protein.

In a preferred embodiment, the invention provides for treatment of various diseases and disorders by administration of a therapeutic compound (termed herein "Therapeutic"). Such "Therapeutics" include but are not limited to: GIT transport receptor-binding proteins, and analogs and derivatives (including fragments) thereof (*e.g.*, as described hereinabove) that bind to GIT transport receptors, bound to an active agent of value in the treatment or prevention of a disease or disorder (preferably a mammalian, most preferably human, disease or disorder). Therapeutics also include but are not limited to nucleic acids encoding the GIT transport receptor-binding proteins, analogs, or derivatives bound to such a therapeutic or prophylactic active agent. The active agent is preferably a drug.

Any drug known in the art may be used, depending upon the disease or disorder to be treated or prevented, and the type of subject to which it is to be administered. As used herein, the term "drug" includes, without limitation, any pharmaceutically active agent. Representative drugs include, but are not limited to, peptides or proteins, hormones, analgesics, anti-migraine agents, anti-coagulant agents, anti-emetic agents, cardiovascular agents, anti-hypertensive agents, narcotic antagonists, chelating agents, anti-anginal agents, chemotherapy agents, sedatives, anti-neoplastics, prostaglandins, and antidiuretic agents. Typical drugs include peptides, proteins or hormones such as

insulin, calcitonin, calcitonin gene regulating protein, atrial natriuretic protein, colony stimulating factor, betaseron, erythropoietin (EPO), interferons such as α, β or γ interferon, somatropin, somatotropin, somatostatin, insulin-like growth factor (somatomedins), luteinizing hormone releasing hormone (LHRH), tissue plasminogen activator (TPA), growth hormone releasing hormone (GHRH), oxytocin, estradiol, growth hormones, leuprolide acetate, factor VIII, interleukins such as interleukin-2, and analogs thereof; analgesics such as fentanyl, sufentanil, butorphanol, buprenorphine, levorphanol, morphine, hydromorphone, hydocodone, oxymorphone, methadone, lidocaine, bupivacaine, diclofenac, naproxen, paverin, and analogs thereof; anti-migraine agents such as heparin, hirudin, and analogs thereof; anti-coagulant agents such as scopolamine, ondansetron, domperidone, etoclopramide, and analogs thereof; cardiovascular agents, anti-hypertensive agents and vasodilators such as diltiazem, clonidine, nifedipine, verapamil, isosorbide-5-mononitrate, organic nitrates, agents used in treatment of heart disorders and analogs thereof; sedatives such as benzodiazeines, phenothiozines and analogs thereof; narcotic antagonists such as naltrexone, naloxone and analogs thereof; chelating agents such as deferoxamine and analogs thereof; anti-diuretic agents such as desmopressin, vasopressin and analogs thereof; anti-anginal agents such as nitroglycerine and analogs thereof; anti-neoplastics such as 5-fluorouracil, bleomycin and analogs thereof; prostaglandins and analogs thereof; and chemotherapy agents such as vincristine and analogs thereof. Representative drugs also include but are not limited to antisense oligonucleotides, genes, gene correcting hybrid oligonucleotides, ribozymes, aptameric oligonucleotides, triple-helix forming oligonucleotides, inhibitors of signal transduction pathways, tyrosine kinase inhibitors and DNA modifying agents. Drugs that can be used also include, without limitation, systems containing gene therapeutics, including viral systems for therapeutic gene delivery such as

adenovirus, adeno-associated virus, retroviruses, herpes simplex virus, sindbus virus, liposomes, cationic lipids, dendrimers, and enzymes. For instance, gene delivery viruses can be modified such that they express the targeting peptide on the surface so as to permit targeted gene delivery.

In a preferred embodiment, a Therapeutic is therapeutically or prophylactically administered to a human patient.

Additional descriptions and sources of Therapeutics that can be used according to the invention are found in various Sections herein.

5.7. Therapeutic/Prophylactic Administration, Compositions and Formulations

The invention provides methods of treatment (and prophylaxis) by administration to a subject of an effective amount of a Therapeutic of the invention. In a preferred aspect, the Therapeutic is substantially purified. The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably a human.

As will be clear, any disease or disorder of interest amenable to therapy or prophylaxis by providing a drug *in vivo* systemically or by targeting a drug *in vivo* to the GIT (by linkage to a GIT transport-receptor binding protein, derivative or analog of the invention) can be treated or prevented by administration of a Therapeutic of the invention. Such diseases may include but are not limited to hypertension, diabetes, osteoporosis, hemophilia, anemia, cancer, migraine, and angina pectoris, to name but a few.

Any route of administration known in the art may be used, including but not limited to oral, nasal, topical, intravenous, intraperitoneal, intradermal, mucosal, intrathecal, intramuscular, etc. Preferably, administration is oral; in such an embodiment the GIT-transport binding protein, derivative or analog of the invention acts

advantageously to facilitate transport of the therapeutic active agent through the lumen of the GIT into the systemic circulation.

The present invention also provides therapeutic compositions/formulations. In a specific embodiment of the invention, a GIT transport receptor-binding peptide or motif of interest is associated with a therapeutically or prophylactically active agent, preferably a drug or drug-containing nano- or microparticle. More preferably, the active agent is a drug encapsulating or drug loaded nano- or microparticle, such as a biodegradable nano- or microparticle, in which the peptide is physically adsorbed or coated or covalently bonded, such as directly linked or linked via a linking moiety, onto the surface of the nano- or microparticle. Alternatively, the peptide can form the nano- or microparticle itself or can be directly conjugated to the active agent. Such conjugations include fusion proteins in which a DNA sequence coding for the peptide is fused in-frame to the gene or cDNA coding for a therapeutic peptide or protein, such that the modified gene codes for a recombinant fusion protein in which the "targeting" peptide is fused to the therapeutic peptide or protein and where the "targeting" peptide increases the absorption of the fusion protein from the GIT. Preferably the particles range in size from 200-600 nm.

Thus, in a specific embodiment, a GIT transport-binding protein is bound to a slow-release (controlled release) device containing a drug. In a specific embodiment, polymeric materials can be used (*see* Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J. Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); *see also* Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J. Neurosurg. 71:105 (1989)).

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a Therapeutic, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulations can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the Therapeutic, preferably in purified

form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient.

The Therapeutics of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the Therapeutic of the invention which will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances.

6. EXAMPLES

6.1. Selection of GIT Receptor Targets

The HPT1, hPEPT1, D2H, and hSI receptors were selected for cloning as GIT receptor targets based on several criteria, including: (1) expression on surface of epithelial cells in gastro-intestinal tract (GIT); (2) expression along the length of small intestine (HPT1, hPEPT1, D2H); (3) expression locally at high concentration (hSI); (4) large putative extracellular domains facing into the lumen of the GIT; and (5) extracellular domains that permit easy access and bioadhesion by targeting particles.

The four recombinant receptor sites screened with the peptide libraries additionally have the following characteristics:

Receptor	Characteristics
D2H	Transport of neutral/basic amino acids; a transport activating protein for a range of amino acid translocases
hSI	Metabolism of sucrose and other sugars; represents 9% of brush border membrane protein in Jejunum
HPT1	di/tri peptide transporter or facilitator of peptide transport
hPEPT1	di/tri peptide transporter

Figures 1-4 (SEQ ID NOS:176, 178, 179, and 181, respectively) show the predicted amino acid sequences for hPEPT1, HPT1, hSI and D2H, respectively.

6.2. Cloning of Extracellular Domain of Selected Receptor Site

The following receptor domains were cloned and expressed as His-tag fusion proteins by standard techniques:

Receptor	**Domain (amino acid residues)**
hPEPT1[a]	391-571
HPT1[b]	29-273
hSI[c]	272-667
D2H[d]	387-685

[a] Liang et al., 1995, J. Biol. Chem. 270:6456-6463
[b] Dantzig et al., 1994, Association of Intestinal Peptide Transport with a Protein Related to the Cadherin Superfamily
[c] Chantret et al., Biochem. J. 285:915-923
[d] Bertran et al., J. Biol. Chem. 268:14842-14949

The receptor proteins were expressed as His-tag fusion proteins and affinity purified under denaturing conditions, using urea or guanidine HCl, utilizing the pET His-tag metal chelate affinity for Ni-NTA Agarose (Hochuli, E., Purification of recombinant proteins with metal chelate adsorbent, Genetic Engineering, Principals and Methods (J.K. Setlow, ed.), Plenum Press, NY, Vol. 12 (1990), pp. 87-98).

6.3. Phage Libraries

Three phage DC8, D38, and DC43 libraries expressing N-terminal pIII fusions in M13 were used to identify peptides that bind to the GIT receptors. The D38 and DC43 libraries which are composed of 37 and 43 random amino acid domains, respectively, have been described previously (McConnell et al., 1995, Molecular Diversity, 1:165-176). The DC8 library is similar to the other two except that the random insert is 8 amino acids long flanked on each side by a cysteine residue (*i.e.*, CX_8C).

6.4. Biopanning

Three rounds of biopanning on the GIT receptors were performed generally by standard methods (McConnell et al., 1995, Molecular Diversity, 1:165-176), using a mixture of the DC8 (1×10^{10} pfu), D38 and DC43 (1×10^{11} pfu) phage libraries. After each round of panning the percentage of phage recovered was determined. Following the first two rounds of panning, the eluted phage were amplified overnight. Phage from the third pan were plated out and 100 plaques were picked, amplified overnight and screened in an ELISA assay for binding to the relevant receptor and BSA. After data analysis, phage clones were identified which had high absorbance in the ELISA assay and/or a good ratio of binding to target compared to binding to BSA. The Insulin Degrading Enzyme (IDE) and recombinant human tissue factor (hTF) were used as irrelevant controls. Several variations of the standard panning technique, discussed below, were used. Selection or panning methods followed one of two strategies. The first strategy involved panning the mixed libraries on the specific GIT receptor adsorbed to a solid surface. The second strategy panned the libraries twice against the GIT receptor and then against Caco-2 cells (Peterson and Mooseker, 1992, J. Cell Science 102:581-600), Selection methods are reflected in the clone nomenclature as described below:

S designates the clone was identified by binding to the hS1 receptor domain.

D designates the clone was identified by binding to the D2H receptor domain.

P designates the clone was identified by binding to the PEPT1 receptor domain.

H designates the clone was identified by binding to the HPT-1 receptor domain.

Phage designated Ni are from a solid phase band GIT receptor pan that used the standard procedure with the addition of Ni-NTA Agarose (Qiagen, Chatsworth, CA). Receptor coated plates were blocked with 0.5% BSA/PBS containing 160μl Ni-NTA agarose and libraries were panned in the presence of 50μl Ni-NTA agarose. The receptor proteins were expressed as His-tag fusions. The His-tag has a high affinity for Ni-NTA Agarose. Blocking the plate and panning in the presence of Ni-NTA agarose minimized phage binding to the His-tag portion of the recombinant receptor.

Phage with the designation AX were eluted with acid and Factor Xa. Phage were first eluted by standard acid elution then Factor Xa (New England Biolabs, Beverly, MA: 1μg protease in 300μl of 20mM Tris-HCL, 100mM NaCl, 2mM $CaCl_2$) was added to the panning plate and incubated 2 hours. Phage from both elution methods were pooled together then plated.

Phage with the designation AB were eluted with acid and base. Phage were eluted first by standard acid elution then 100mM triethylamine pH 12.1 was added to the panning plate for 10 minutes. Phage from both elution methods were pooled together then plated.

C designates panning on receptor followed by Caco-2 cells. First and second round pans were performed on the receptor and the third round pan was on snapwells of Caco-2 cells. DCX11, DCX8 and DCX33 were identified by two pans on D2H receptor, third pan on Caco-2 cells. The third round Factor Xa eluate from the Caco-2 cells was screened by ELISA on D2H, BSA and fixed Caco-2 cells. For HCA3 the first two rounds of panning were performed on the HPT-1 receptor and

the third pan was on monolayers cultured on snapwells of Caco-2 cells.

Phage designated 5PAX were carried through five rounds of panning after which a number of phage were sequenced prior to screening by ELISA.

6.5. Sequencing of Selected Phage

The amino acid sequence of phage inserts demonstrating a good ratio of binding to receptor domains and/or Caco-2 cells over background BSA binding were deduced from the nucleotide sequence obtained by sequencing (Sequenase®, U.S. Biochemical Corp., Cleveland, OH) both DNA strands of the appropriate region in the viral genome. The third round acid eluate was screened by ELISA on HPT-1, BSA and Caco-2 fixed cells. Phage designated 5PAX were carried through five rounds of panning after which a number of phages were sequenced prior to screening by ELISA.

One well of a 24 well plate was coated with 10 μg/ml of GIT receptor and the plate was incubated overnight at 4°C. The plate was blocked with 0.5 BSA-PBS for one hour. A mixture of the DC8, D38 and DC43 phage libraries was added to the plate and the plate was incubated for 2 to 3 hours at room temperature on a rotator. After washing the well 10 times with 1% BSA plus 0.05% Tween 20 in PBS, the well was eluted with 0.05m glycine, pH2. The phage was then eluted with 0.2M $NaPO_4$. The eluted phage was titered on agar plates; the remaining phage was amplified overnight. The next day the amplified phage was added to a second coated plate and the panning procedure was repeated as described above. The eluted phage from the second pan as well as the amplified phage from the first pan was titered on agar plates. Following amplification overnight of the phage from the second pan, the panning procedure was repeated as described above. The phage eluted from the third pan and the amplified phage from the second pan were then titered overnight on agar plates. Isolated phage colonies were amplified overnight prior to use in an ELISA assay.

6.6. Receptor ELISA Procedure

96 well plates were coated overnight with GIT receptor, BSA and, optionally, IDE (insulin degrading enzyme, an irrelevant His-fusion protein)or hTF. The plates were blocked for one hour with 0.5% BSA-PBS. After clarification, the amplified phage were diluted 1:100 in 1% BSA plus 0.05% Tween 20 in PBS and added to the plates. Following incubation of the plates on a rotator for 1 to 2 hours, the plates were washed 5 times with 1% BSA plus 0.05% Tween 20 in PBS. Dilute anti-M13-HRP conjugate (anti-M13 antibody linked to horse radish peroxidase (HRP)) was added to all the wells and the plate was incubated for one hour on a rotator. After the plates were washed 5 times, as described above, TMB substrate was added to the wells. The plates were read at 650nm absorbance.

RECEPTOR ELISA RESULTS:

Below are the results of ELISA assays which assessed the binding of phage panned on the hSI receptor to microtiter plates coated with hSI and BSA. Table 1 shows the OD results as well as the ratio of hSI to BSA binding.

Table 1

PHAGE	hSI	BSA	hSI/BSA
S15	0.478	0.053	9
S21	0.845	0.092	9
S22	0.399	0.061	7
SNi10	0.57	0.051	11
SNi28	0.942	0.113	8
SNi34	0.761	0.115	7
SNi38	0.466	0.076	6
SNi45	0.518	0.056	9
SNiAX2	0.383	0.065	6
SNiAX6	0.369	0.056	7
SNiAX8	0.342	0.068	5
BLANK	0.063	0.042	2

Below are the results of an ELISA which assessed the binding of phage panned on the D2H receptor to microtiter plates coated with D2H and BSA. Table 2 shows the OD results as well as the ratio of D2H to BSA binding.

Table 2

Phage	D2H	BSA	D2H/BSA
DAB3	0.406	0.072	6
DAB7	0.702	0.09	8
DAB10	0.644	0.153	4
DAB18	0.467	0.085	5
DAB24	1.801	0.441	4
DAB30	0.704	0.121	6
DAX15	0.391	0.101	4
DAX23	0.698	0.153	5
DAX24	0.591	0.118	5
DAX27	1.577	0.424	4
BLANK	0.038	0.037	1

Below are the results of an ELISA which assessed the binding of phage panned for two rounds on the D2H receptor followed by a third round pan on Caco-2 snapwells. Binding to fixed Caco-2 cells, D2H and BSA was examined.

Table 3 shows the OD results as well as the ratio of D2H to BSA binding.

Table 3

PHAGE	Caco-2	D2H	BSA	D2H/BSA
DCX8	0.498	0.163	0.063	3
DCX11	0.224	0.222	0.071	3
DCX26	0.114	0.956	0.213	4
DCX33	0.164	0.616	0.103	6
DCX36	0.149	0.293	0.064	5
DCX39	0.121	0.299	0.066	5
DCX42	0.308	0.158	0.065	2
DCX45	0.147	0.336	0.075	4
Blank	0.065	0.043	0.04	1

Below are the results of an ELISA which assessed the binding of phage panned on the hPEPT1 receptor to hPEPT1 and BSA. Table 4 shows the OD results as well as the ratio of hPEPT1 to BSA binding.

Table 4

PHAGE	hPEPT1	BSA	PEPT1/BSA
PAX9	0.312	0.079	4
PAX14	1.102	0.139	8
PAX15	0.301	0.079	4
PAX16	0.648	0.171	4
PAX17	0.514	0.095	5
PAX18	0.416	0.087	5
PAX35	0.474	0.065	7
PAX38	0.292	0.064	5
PAX40	0.461	0.076	6
PAX43	0.345	0.069	5
PAX45	0.419	0.081	5
PAX46	0.429	0.077	6
P31	0.807	0.075	11
P90	1.117	0.107	9
5PAX3	0.173	0.04	4
5PAX5	0.15	0.036	4
5PAX7	0.171	0.037	5
5PAX12	0.227	0.04	6
Blank	0.102	0.039	3

Table 5 shows the results of an ELISA which assessed the binding of phage panned on the HPT-1 receptor to HPT-1 and BSA. The table shows the OD results as well as the ratio of HPT-1 to BSA binding.

Table 5

PHAGE	HPT1	BSA	HPT/BSA
HAX9	0.382	0.075	5
HAX40	0.991	0.065	15
HAX42	0.32	0.071	5

Table 6 shows the results of an ELISA which assessed the binding of phage panned for two rounds on the HPT-1 receptor followed by a third round pan on Caco-2 snapwells. Binding to fixed Caco-2 cells, HPT-1 and BSA was examined. The table shows the OD results as well as the ratio of HPT-1 to BSA binding.

Table 6

PHAGE	Caco-2	HPT1	BSA	HPT1/BSA
HCA3	0.406	0.048	0.038	1

CELL ELISA PROCEDURE

Phage ELISA was used as described above with the following changes. Diluent and wash buffer was PBS containing 1%BSA and 0.05% Tween 20 and plates were washed five times at each wash step. Supernatant of infected bacterial cultures was diluted 1:100 and incubated with protein coated plates for 2-3 hours with mild agitation. Anti-M13 Horseradish peroxidase (HRP) conjugate (Pharmacia, Piscataway, NJ) was diluted 1:8000.

Fixed Caco-2, C2BBe1, and A431 cell plates were prepared by growing cells on tissue culture treated microtiter plates. When cells were confluent, plates were fixed with 10% formaldehyde, washed twice with PBS and stored with 0.5%BSA-PBS at -20°C. On the day of the assay, thawed

plates were treated with PBS containing 0.1% phenylhydrazine for one hour at 37°C followed by two PBS washes and blocking for One hour with 0.5%BSA-PBS. The standard ELISA procedure was followed at this point.

Phage which showed specificity to a GIT receptor was further characterized by ELISA on a variety of recombinant proteins. Phage which continued to exhibit GIT receptor specificity was sequenced.

Table 7

TARGET BINDING PHAGE INSERT SEQUENCES:

hSI	SEQ. ID. NO.	
S15	1	RSGAYESPDGRGGRSYVGGGGGCGNIGRKHNLWGLRTASPACWD
S21	2	SPRSFWPVVSRHESFGISNYLGCGYRTCISGTMTKSSPIYPRHS
S22	3	SSSSDWGGVPGKVVRERFKGRGCGISITSVLTGKPNPCPEPKAA
SNi10	4	RVGQCTDSDVRRPWARSCAHQGCGAGTRNSHGCITRPLRQASAH
SNi28	5	SHSGGMNRAYGDVFRELRDRWNATSHHTRPTPQLPRGPN
SNi34	6	SPCGGSWGRFMQGGLFGGRTDGCGAHRNRTSASLEPPSSDY
SNi38	7	RGAADQRRGWSENLGLPRVGWDAIAHNSYTFTSRRPRPP
SNi45	8	SGGEVSSWGRVNDLCARVSWTGCGTARSARTDNKGFLPKHSSLR
SNiAX2	9	SDSDGDHYGLRGGVRCSLRDRGCGLALSTVHAGPPSFYPKLSSP
SNiAX4	10	RSLGNYGVTGTVDVTVLPMPGHANHLGVSSASSSDPPRR
SNiAX6	11	RTTTAKGCLLGSFGVLSGCSFTPTSPPPHLGYPPHSVN
SNiAX8	12	SPKLSSVGVMTKVTELPTEGPNAISIPISATLGPRNPLR
D2H		
DAB3	13	RWCGAELCNSVTKKFRPGWRDHANPSTHHRTPPPSQSSP
DAB7	14	RWCGADDPCGASRWRGGNSLFGCGLRCSAAQSTPSGRIHSTSTS
DAB10	15	SKSGEGGDSSRGETGWARVRSHAMTAGRFRWYNQLPSDR
DAB18	16	RSSANNCEWKSDWMRRACIARYANSSGPARAVDTKAAP
DAB24	17	SKWSWSSRWGSPQDKVEKTRAGCGGSPSSTNCHPYTFAPPPQAG
DAB30	18	SGFWEFSRGLWDGENRKSVRSGCGFRGSSAQGPCPVTPATIDKH
DAX15	19	SESGRCRSVSRWMTTWQTQKGGCGSNVSRGSPLDPSHQTGHATT
DAX23	20	REWRFAGPPLDLWAGPSLPSFNASSHPRALRTYWSQRPR
DAX24	21	RMEDIKNSGWRDSCRWGDLRPGCGSRQWYPSNMRSSRDYPAGGH
DAX27	22	SHPWYRHWNHGDFSGSGQSRHTPPESPHPGRPNATI

DCX8	23	RYKHDIGCDAGVDKKSSSVRGGCGAHSSPPRAGRGPRGTMVSRL
DCX11	24	SQGSKQCMQYRTGRLTVGSEYGCGMNPARHATPAYPARLLPRYR
DCX26	25	SGRTTSEISGLWGWGDDRSGYGWGNTLRPNYIPYRQATNRHRYT
DCX33	26	RWNWTVLPATGGHYWTRSTDYHAINNHRPSIPHQHPTPI
DCX36	27	SWSSWNWSSKTTRLGDRATREGCGPSQSDGCPYNGRLTTVKPRT
DCX39	28	SGSLNAWQPRSWVGGAFRSHANNNLNPKPTMVTRHPT
DCX42	29	RYSGLSPRDNGPACSQEATLEGCGAQRLMSTRRKGRNSRPGWTL
DCX45	30	SVGNDKTSRPVSFYGRVSDLWNASLMPKRTPSSKRHDDG

<u>hPEPT1</u>

PAX9	31	RWPSVGYKGNGSDTIDVHSNDASTKRSLIYNHRRPLFP
PAX14	32	RTFENDGLGVGRSIQKKSDRWYASHNIRSHFASMSPAGK
PAX15	33	SYCRVKGGGEGGHTDSNLARSGCGKVARTSRLQHINPRATPPSR
PAX16	34	SWTRWGKHTHGGFVNKSPPGKNATSPYTDAQLPSDQGPP
PAX17	35	SQVDSFRNSFRWYEPSRALCHGCGKRDTSTTRIHNSPSDSYPTR
PAX18	36	SFLRFQSPRFEDYSRTISRLRNATNPSNVSDAHNNRALA
PAX35	37	RSITDGGINEVDLSSVSNVLENANSHRAYRKHRPTLKRP
PAX38	38	SSKVSSPRDPTVPRKGGNVDYGCGHRSSARMPTSALSSITKCYT
PAX40	39	RASTQGGRGVAPEFGASVLGRGCGSATYYTNSTSCKDAMGHNYS
PAX43	40	RWCEKHKFTAARCSAGAGFERDASRPPQPAHRDNTNRNA
PAX45	41	SFQVYPDHGLERHALDGTGPLYAMPGRWIRARPQNRDRQ
PAX46	42	SRCTDNEQCPDTGTRSRSVSNARYFSSRLLKTHAPHRP
P31	43	SARDSGPAEDGSRAVRLNGVENANTRKSSRSNPRGRRHP
P90	44	SSADAEKCAGSLLWWGRQNNSGCGSPTKKHLKHRNRSQTSSSSH
5PAX3	45	RPKNVADAYSSQDGAAAEETSHASNAARKSPKHKPLRRP
5PAX5	46	RGSTGTAGGERSGVLNLHTRDNASGSGFKPWYPSNRGHK
5PAX7	47	RWGWERSPSDYDSDMDLGARRYATRTHRAPPRVLKAPLP
5PAX12	48	RGWKCEGSQAAYGDKDIGRSRGCGSITKNNTNHAHPSHGAVAKI

<u>HPT-1</u>

HAX9	49	SREEANWDGYKREMSHRSRFWDATHLSRPRRPANSGDPN
HAX35	50	EWYSWKRSSKSTGLGDTATREGCGPSQSDGCPYNGRLTTVKPRK
HAX40	51	REFAERRLWGCDDLSWRLDAEGCGPTPSNRAVKHRKPRPRSPAL
HAX42	52	SDHALGTNLRSDNAKEPGDYNCCGNGNSTGRKVFNRRRPSAIPT
HCA3	53	RHISEYSFANSHLMGGESKRKGCGINGSFSPTCPRSPTPAFRRT
H40	54	SRESGMWGSWWRGHRLNSTGGNANMNASLPPDPPVSTP
PAX2	55	STPPSREAYSRPYSVDSDSDTNAKHSSHNRRLRTRSRPN

Table 8

DNA Sequences for Clones used in *in vivo* Pan

S15 (SEQ ID NO: 56)

TCTCACTCCTCGAGATCCGGCGCTTATGAGAGTCCGGATGGTCGGGGGGGTCGGAGCTATG
TGGGGGGCGGGGGTGGNTGTGGTAACATTGGTCGGAAGCATAACCTGTGGGGGCTGCGTAC
CGCGTCGCCGGCCTGCTGGGACTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

S21 (SEQ ID NO: 57)

TCTCACTCCTCGAGTCCTCGCTCTTTCTGGCCCGTTGTGTCCCGGCATGAGTCGTTTGGGA
TCTCTAACTATTTGGGNTGTGGTTATCGTACATGTATCTCCGGCACGATGACTAAGTCTAG
CCCGATTTACCCTCGGCATTCGTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

S22 (SEQ ID NO: 58)

TCTCACTCCTCGAGTAGTAGCTCCGATTGGGGTGGTGTGCCTGGGAAGGTGGTTAGGGAGC
GCTTTAAGGGGCGCGGTTGTGGTATTTCCATCACCTCCGTGCTCACTGGGAAGCCCAATCC
GTGTCCGGAGCCTAAGGCGGCCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

SNi 10 (SEQ ID NO: 59)

TCTCACTCCTCGAGAGTTGGCCAGTGCACGGATTCTGATGTGCGGCGTCCTTGGGCCAGGT
CTTGCGCTCATCAGGGTTGTGGTGCGGGCACTCGCAACTCGCACGGCTGCATCACCCGTCC
TCTCCGCCAGGCTAGCGCTCATTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

SNi 28 (SEQ ID NO: 60)

TCTCACTCCTCGAGCCACTCCGGTGGTATGAATAGGGCCTACGGGGATGTGTTTAGGGAGC
TTCGTGATCGGTGGAACGCCACTTCCCACCACACTCGCCCCACCCCTCAGCTCCCCCGTGG
GCCTAATTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

SNi 34 (SEQ ID NO: 61)

TCTCACTCCTCGAGTCCGTGCGGGGGGTCGTGGGGGCGTTTTATGCAGGGTGGCCTTTTCG
GCGGTAGGACTGATGGTTGTGGTGCCCATAGAAACCGCACTTCTGCGTCGTTAGAGCCCCC
GAGCAGCGACTACTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

SNi 38 (SEQ ID NO: 62)

TCTCACTCCTCGAGGGGCGCCGCCGATCAGCGGCGGGGGTGGTCCGAGAACTTGGGGTTGC
CTAGGGTGGGGTGGGACGCCATCGCTCACAATAGCTATACGTTCACCTCGCGCCGCCCGCG
CCCCCCCTCTAGA

SNi 45 (SEQ ID NO: 63)

TCTCACTCCTCGAGCGGTGGGGAGGTCAGCTCCTGGGGCCGCGTGAATGACCTCTGCGCTA
GGGTGAGTTGGACTGGTTGTGGTACTGCTCGTTCCGCGCGTACCGACAACAAAGGCTTTCT
TCCTAAGCACTCGTCACTCCGCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

SNi AX2 (SEQ ID NO: 64)

TCTCACTCCTCGAGTGATAGTGACGGGGATCATTATGGGCTTCGGGGGGGGTGCGTTGTT
CGCTTCGTGATAGGGGTTGTGGTCTGGCCCTGTCCACCGTCCATGCTGGTCCCCCCTCTTT
TTACCCCAAGCTCTCCAGCCCCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

SNi AX4 (SEQ ID NO: 65)

TCTCACTCCTCGAGGAGCTTGGGTAATTATGGCGTCACCGGGACTGTGGACGTGACGGTTT
TGCCCATGCCTGGCCACGCCAACCACCTTGGTGTCTCCTCCGCCTCTAGCTCTGATCCTCC
GCGGCGCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

SNi AX6 (SEQ ID NO: 66)

TCTCACTCCTCGAGAACTACGACGGCTAAGGGGTGTCTTCTCGGAAGCTTCGGCGTTCTTA
GTGGGTGCTCATTTACGCCAACCTCTCCACCGCCCCACCTAGGATACCCCCCCCACTCCGT
CAATTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

SNi AX8 (SEQ ID NO: 67)

TCTCACTCCTCGAGCCCGAAGTTGTCCAGCGTGGGTGTTATGACTAAGGTCACGGAGCTGC
CCACGGAGGGGCCTAACGCCATTAGTATTCCGATCTCCGCGACCCTCGGCCCGCGCAACCC
GCTCCGCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DAB3 (SEQ ID NO: 68)

TCTCACTCCTCGAGGTGGTGCGGCGCTGAGCTGTGCAACTCGGTGACTAAGAAGTTTCGCC
CGGGCTGGCGGGATCACGCCAATCCCTCCACCCATCATCGTACTCCCCCGCCCAGCCAGTC
CAGCCCTTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DAB7 (SEQ ID NO: 69)

TCTCACTCCTCGAGGTGGTGCGGCGCTGATGACCCGTGTGGTGCCAGTCGTTGGCGGGGGG
GCAACAGCTTGTTTGGTTGTGGTCTTCGTTGTAGTGCGGCGCAGAGCACCCCGAGTGGCAG
GATCCATTCCACTTCGACCAGCTCTAGAATCGAAGGTGCGCTAGACCTTCGAGA

DAB10 (SEQ ID NO: 70)

TCTCACTCCTCGAGTAAGTCCGGGGAGGGGGGTGACAGTAGCAGGGGCGAGACGGGCTGGG
CGAGGGTTCGGTCTCACGCCATGACTGCTGGCCGCTTTCGGTGGTACAACCAGTTGCCCTC
TGATCGGTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DAB18 (SEQ ID NO: 71)

TCTCACTCCTCGAGGTCGAGCGCCAATAATTGCGAGTGGAAGTCTGATTGGATGCGCAGGG
CCTGTATTGCTCGTTACGCCAACAGTTCGGGCCCCGCCCGCGCCGTCGACACTAAGGCCGC
GCCCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DAB24 (SEQ ID NO: 72)

TCTCACTCCTCGAGTAAGTGGTCGTGGAGTTCGAGGTGGGGCTCCCCGCAGGATAAGGTTG
AGAAGACCAGGGCGGGTTGTGGTGGTAGTCCCAGCAGCACCAATTGTCACCCCTACACCTT
TGCCCCCCCCCCGCAAGCCGGCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DAB30 (SEQ ID NO: 73)

TCTCACTCCTCGAGTGGGTTCTGGGAGTTTAGCAGGGGGCTTTGGGATGGGGAGAACCGTA
AGAGTGTCCGGTCGGGTTGTGGTTTTCGTGGCTCCTCTGCTCAGGGCCCGTGTCCGGTCAC
GCCTGCCACCATTGACAAACACTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DAX15 (SEQ ID NO: 74)

TCTCACTCCTCGAGTGAGAGCGGGCGGTGCCGTAGCGTGAGCCGGTGGATGACGACGTGGC
AGACGCAGAAGGGCGGTTGTGGTTCCAATGTTTCCCGCGGTTCGCCCCTCGACCCCTCTCA
CCAGACCGGGCATGCCACTACTTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DAX23 (SEQ ID NO: 75)

TCTCACTCCTCGAGGGAGTGGAGGTTTGCCGGGCCGCCGTTGGACCTGTGGGCGGGTCCGA
GCTTGCCCTCTTTTAACGCCAGTTCCCACCCTCGCGCCCTGCGCACCTATTGGTCCCAGCG
GCCCCGCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DAX24 (SEQ ID NO: 76)

TCTCACTCCTCGAGGATGGAGGACATCAAGAACTCGGGGTGGAGGGACTCTTGTAGGTGGG
GTGACCTGAGGCCTGGTTGTGGTAGCCGCCAGTGGTACCCCTCGAATATGCGTTCTAGCAG
AGATTACCCCGCGGGGGGCCACTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DAX27 (SEQ ID NO: 77)

TCTCACTCCTCGAGTCATCCGTGGTACAGGCATTGGAACCATGGTGACTTCTCTGGTTCGG
GCCAGTCACGCCACACCCCGCCGGAGAGCCCCCACCCCGGCCGCCCTAATGCCACCATTTC
TAGAATCGAAGGTCGCGCTAGACCTTCGAG

DCX8 (SEQ ID NO: 78)

TCTCACTCCTCGAGATATAAGCACGATATCGGTTGCGATGCTGGGGTTGACAAGAAGTCGT
CGTCTGTGCGTGGTGGTTGTGGTGCTCATTNGTCGCCACCCCGCGCCGGCCGTGGTCCTCG
CGGCACGATGGTTAGCAGGCTTTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DCX11 (SEQ ID NO: 79)

TCTCACTCCTCGAGTCAGGGCTCCAAGCAGTGTATGCAGTACCGCACCGGTCGTTTGACGG
TGGGGTCTGAGTATGGTTGTGGTATGAACCCCGCCCGCCATGCCACGCCCGCTTATCCGGC
GCGCCTGCTGCCACGCTATCGCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DCX26 (SEQ ID NO: 80)

TCTCACTCCTCGAGTGGGCGGACTACTAGTGAGATTTCTGGGCTCTGGGGTTGGGGTGACG
ACCGGAGCGGTTATGGTTGGGGTAACACGCTCCGCCCCAACTACATCCCTTATAGGCAGGC
GACGAACAGGCATCGTTATACGTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DCX33 (SEQ ID NO: 81)

TCTCACTCCTCGAGGTGGAATTGGACTGTCTTGCCCGCCACTGGCGGCCATTACTGGACGC
GTTCGACGGACTATCACGCCATTAACAATCACAGGCCGAGCATCCCCCACCAGCATCCGAC
CCCTATCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DCX36 (SEQ ID NO: 82)

TCTCACTCCTCGAGTTGGTCGTCGTGGAATTGGAGCTCTAAGACTACTCGTCTGGGCGACA
GGGCGACTCGGGAGGGTTGTGGTCCCAGCCAGTCTGATGGCTGTCCTTATAACGGCCGCCT
TACGACCGTCAAGCCTCGCACGTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DCX39 (SEQ ID NO: 83)

TCTCACTCCTCGAGTGGTAGTTTGAACGCATGGCAACCGCGGTCATGGGTGGGGGGCGCGT
TCCGGTCACACGCCAACAATAACTTGAACCCCAAGCCCACCATGGTTACTNGTCACCCTAC
CTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

DCX42 (SEQ ID NO: 84)

TCTCACTCCTCGAGGTATTCGGGTTTGTCCCCGCGGGACAACGGTCCCGCTTGTAGTCAGG
AGGCTACCTTGGAGGGTTGTGGTGCGCAGAGGCTGATGTCCACCCGTCGCAAGGGCCGCAA
CTCCCGCCCCGGGTGGACGCTCTCTAGAATCGAAGGTCGCGCTAGACCCTTCGAGA

DCX45 (SEQ ID NO: 85)

TCTCACTCCTCGAGCGTGGGGAATGATAAGACTAGCAGGCCGGTTTCCTTCTACGGGCGCG
TTAGTGATCTGTGGAACGCCAGCTTGATGCCGAAGCGTACTCCCAGCTCGAAGCGCCACGA
TGATGGCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

PAX2 (SEQ ID NO: 86)

TCTCACTCCTCGAGTACTCCCCCCAGTAGGGAGGCGTATAGTAGGCCCTATAGTGTCGATA
GCGATTCGGATACGAACGCCAAGCACAGCTCCCACAACCGCCGTNTGCGGACGCGCAGCCG
CCCGAACTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

PAX9 (SEQ ID NO: 87)

TCTCACTCCTCGAGATGGCCTAGTGTGGGTTACAAGGGTAATGGCAGTGACACTATTGATG
TTCACAGCAATGACGCCAGTACTAAGAGGTCCCTCATCTATAACCACCGCCGCCCCNTCTT
TCCCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

PAX14 (SEQ ID NO: 88)

TCTCACTCCTCGAGAACGTTTGAGAACGACGGGCTGGGCGTCGGCCGGTCTATTCAGAAGA
AGTCGGATAGGTGGTACGCCAGCCACAACATTCGTAGCCATTTCGCGTCCATGTCTCCCGC
TGGTAAGTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

PAX15 (SEQ ID NO: 89)

TCTCACTCCTCGAGCTATTGTCGGGTTAAGGGTGGTGGGGAGGGGGGCATACGGATTCCA
ATCTGGCTAGGTCGGGTTGTGGTAAGGTGGCCAGGACCAGCAGGCTTCAGCATATCAACCC
GCGCGCTACCCCCCCCTCCCGGTCTAGAATCGAAGGTC

PAX16 (SEQ ID NO: 90)

TCTCACTCCTCGAGTTGGACTCGGTGGGGCAAGCACANTCATGGGGGGTTTGTGAACAAGT
CTCCCCCTGGGAAGAACGCCACGAGCCCCTACACCGACGCCCAGCTGCCCAGTGATCAGGG
TCCTCCCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

PAX17 (SEQ ID NO: 91)

TCTCACTCCTCGAGTCAGGTTGATTCGTTTCGTAATAGCTTTCGGTGGTATGAGCCGAGCA
GGGCTCTGTGCCATGGTTGTGGTAAGCGCGACACCTCCACCACTCGTATCCACAATAGCCC
CAGCGACTCCTATCCTACACGCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

PAX18 (SEQ ID NO: 92)

TCTCACTCCTCGAGCTTTTTGCGGTTCCAGAGTCCGAGGTTCGAGGATTACAGTAGGACGA
TCTNTCGGTTGCGCAACGCCACGAACCCGAGTAATGTCTCCGATGCGCACAATAACCGGGC
CTTGGCCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

PAX35 (SEQ ID NO: 93)

TCTCACTCCTCGAGGAGCATCACCGACGGGGGCATCAATGAGGTGGACCTGAGTAGTGTGT
CGAACGTTCTTGAGAACGCCAACTCGCATAGGGCCTACAGGAAGCATCGCCCGACCTTGAA
GCGTCCTTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

PAX38 (SEQ ID NO: 94)

TCTCACTCCTCGAGTTCGAAGGTGAGCAGCCCGAGGGATCCGACGGTCCCGCGGAAGGGCG
GCAATGTTGATTATGGTTGTGGTCACAGGTCTTCCGCCCGGATGCCTACCTCCGCTCTGTC
GTCGATCACGAAGTGCTACACTTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

PAX40 (SEQ ID NO: 95)

TCTCACTCCTCGAGAGCCAGTANGCAGGGCGGCCGGGGTGTTGCCCCTGAGTTTGGGGCGA
GCGTTTTGGGTNGTGGTTGTGGTAGCGCCACTTATTACACGAACTCCACCAGCTGCAAGGA
TGCTATGGGCCACAACTACTCGTCTAGAATCGAAGGTCGCGNTAGACCTTCGAGA

PAX43 (SEQ ID NO: 96)

TCTCACTCCTCGAGATGGTGCGAGAAGCACAAGTTTACGGCTGCGCGTTGCAGCGCGGGGG
CGGGTTTTGAGAGGGANGCCAGCCGTCCGCCCCAGCCTGCCCACCGGGATAATACCAACCG
TAATGCNTNTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

PAX45 (SEQ ID NO: 97)

TCTCACTCCTCGAGTTTTCAGGTGTACCCGGACCATGGTCTGGAGAGGCATGCTTTGGACG
GGACGGGTCCGCTTTACGCCATGCCCGGCCGCTGGATTAGGGCGCGTCCGCAGAACAGGGA
CCGCCAGTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

PAX46 (SEQ ID NO: 98)

TCTCACTCCTCGAGCAGGTGTACGGACAACGAGCAGTGCCCCGATACCGGGANTAGGTCTC
GTTCCGTTAGTAACGCCAGGTACTTTTCGAGCAGGTTGCTCAAGACTCACGCCCCCCATCG
CCCTTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

P31 (SEQ ID NO: 99)

TCTCACTCCTCGAGTGCCAGGGATAGCGGGCCTGCGGAGGATGGGTCCCGCGCCGTCCGGT
TGAACGGGGTTGAGAACGCCAACACTAGGAAGTCCTCCCGCAGTAACCCGCGGGGTAGGCG
CCATCCCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

P90 (SEQ ID NO: 100)

TCTCACTCCTCGAGTTCCGCCGATGCGGAGAAGTGTGCGGGCAGTCTGTTGTGGTGGGGTA
GGCAGAACAACTCCGGTTGTGGTTCGCCCACGAAGAAGCATCTGAAGCACCGCAATCGCAG
TCAGACCTCCTCTTCGTCCCACTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

5PAX3 (SEQ ID NO: 101)

TCTCACTCCTCGAGACCGAAGAACGTGGCCGATGCTTATTCGTCTCAGGACGGGGCGGCGG
CCGAGGAGACGTCTCACGCCAGTAATGCCGCGCGGAAGTCCCCTAAGCACAAGCCCTTGAG
GCGGCCTTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

5PAX5 (SEQ ID NO: 102)

TCTCACTCCTCGAGAGGCAGTACGGGGACGGCCGGCGGCGAGCGTTCCGGGGTGCTCAACC
TGCACACCAGGGATAACGCCAGCGGCAGCGGTTTCAAACCGTGGTACCCTTCGAATCGGGG
TCACAAGTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

5PAX7 (SEQ ID NO: 103)

TCTCACTCCTCGAGGTGGGGGTGGAGAGGAGTCCGTCCGACTACGATTCTGATATGGACT
TGGGGGCGAGGAGGTACGCCACCCGCACCCACCGCGCGCCCCCTCGCGTCTTGAAGGCTCC
CCTGCCCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

5PAX12 (SEQ ID NO: 104)

TCTCACTCCTCGAGGCACTGGAAGTGCGAGGGCTCTCAGGCTGCCTACGGGGACAAGGATA
TCGGGAGGTCCAGGGGTTGTGGTTCCATTACAAAGAATAACACTAATCACGCCCATCCTAG
CCACGGCGCCGTTGCTAAGATCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

HAX9 (SEQ ID NO: 105)

TCTCACTCCTCGAGCCGCGAGGAGGCGAACTGGGACGGCTATAAGAGGGAGATGAGCCACC
GGAGTCGCTTTTGGGACGCCACCCACCTGTCCCGCCCTCGCCGCCCCGCTAACTCTGGTGA
CCCTAACTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

HAX40 (SEQ ID NO: 106)

TCTCACTCNTCGAGAGAGTTCGCGGAGAGGAGGTTGTGGGGGTGTGATGACCTGAGTTGGC
GTCTCGACGCGGAGGGTTGTGGTCCCACTCCGAGCAATCGGGCCGTCAAGCATCGCAAGCC
CCGCCCACGCTCCCCCGCACTCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

HAX42 (SEQ ID NO: 107)

TCTCACTCNTNGAGTGATCACGCGTTGGGGACGAATCTGAGGTCTGACAATGCCAAGGAGC
CGGGTGATTACAACTGTTGTGGTAACGGGAACTCTACCGGGCGAAAGGTTTTAACCGTAG
GCGCCCCTCCGCCATCCCCANTTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

HCA3 (SEQ ID NO: 108)

TCTCACTCCTCGAGGCATATTTCTGAGTATAGCTTTGCGAATTCCCACTTGATGGGTGGCG
AGTCCAAGCGGAAGGGTTGTGGTATTAACGGCTCCTTTTCTCCCACTTGTCCCCGCTCCCC
CACCCCAGCCTTCCGCCGCACCTCTAGAATCGAAGGTCGCGCTAGACCTTCGAGA

H40 (SEQ ID NO: 109)

TCTCACTCCTCGAGCCGGGAGAGCGGGATGTGGGGTAGTTGGTGGCGTGGTCACAGGTTGA
ATTCCACGGGGGGTAACGCCAACATGAATGCTAGTCTGCCCCCCGACCCCCCTGTTTCCAC
TCCGTCTAGAATCGAAGGTCGCGCTAGACCTTCGAG

Peptide Motifs

By comparison of the amino acid sequences of the clones binding GIT receptors, certain sequence similarities or "motifs" were recognized. These motifs can often represent the part of the sequence that is important for binding to the target. Table 9 identifies regions of sequence similarity or sequence motifs (in boldface) that were identified among GIT binding peptides (corresponding SEQ ID NOS. are shown in Table 7).

Table 9

PEPT-1	
HPT1	
P31	SARDSGPAEDGSRAVRLNGVENAN**TRKS**SRS**N**P**R**GRRHP
PAX9	RWPSVGYKGNGSDTIDVHSNDA**STKRS**LIY**N**H**R**RPLFP
HAX42	SDHALGTNLRSDNAKEPGDYNCCGNGN**ST**GRK-VF**N**R**R**RPSAIPT
PAX2	STPPSREAYSRPYSVDSDSD**T**NA**K**HSSH**N**R**R**LRTRSRPN
hSI	
SNi10	RVGQCT**D**S**D**V**RR**P**W**ARSCAHQGCAGTRNSHGCITRPLRQASAH
SNi38	RGAA**D**Q**RR**G**W**SENLGLPRVGWDAIAHNSYTFTSRRPRPP
S15	RSGAYESP**D**GRGG**R**S**Y**VGGGGGCGNIGRKHNLWGLRTASPACWD
SNi34	SPCGGSWGRFMQGGLFGGRTDGCGAHRNRTSASLEPPSSDY
D2H	
DAB10	**S**KSGEG**G**DSSR**G**ETGWAR**VRS**HAMT**A**GRFRWYNQLPSDR
DAB30	**S**GFWEFSRGLWDGENRK**SVRS**GCGFRG**SS**AQGPCPVTPA**T**IDKH
DCX8	RYKHDI**G**CDA**G**VDKKSS**SVR**GGCG-**A**HS**S**PPRAGRGPRG**T**MVSRL

Phage Binding to Caco-2 Cells

Phage expressing presumed GIT binding peptide inserts were also assayed by ELISA on fixed Caco-2 or C2BBe1 cells as follows. Cells were plated at 1 x 10^5 cells/well on 100 μl culture media and incubated at 30°C in 5% CO_2 overnight. 100 μl 25% formaldehyde was added to each well for 15 minutes. Contents of the wells were removed by inverting the plate. The plate was then washed 3 times with

DPBS. 0.1% phenylhydrazine DPBS solution was added to each well and incubated for 1 hr at 37°C. The plate was inverted and washed 3 times. The plate was blocked with 0.5% BSA-DPBS for 1 hr at room temperature. The plate was inverted and washed 3 times with 1% BPT (PBS containing 1% BSA and 0.05% Tween20). Phage diluted with 1% BPT was added to wells containing fixed cells. Wells without phage added were used to determine background binding of the HRP conjugate. The plates were incubated 2-3 hours on a rotor at room temperature. Plates were washed as before. Plates were incubated with dilute anti-M13-HRP antibody in 1% BPT for 1 hour at room temperature. Following washing, TMB substrate was added and absorbance of the plates were read at 650 nm. Table 10 shows the relative binding of phage encoding peptides to fixed Caco-2 cells.

Table 10.

Relative binding of phage encoding peptides to fixed Caco-2 cells

Phage	Fixed Caco-2 cell binding
SNi10	++
SNi34	+
P31	++
5PAX5	++
PAX2	+
HAX42	+
DCX8	+++
DCX11	+
H1	+
M13mpl18	-

In vivo phage selection:

Further selection of phage expressing peptides capable of binding to the GIT or transporting the GIT was done as follows. The purified library was resuspended in a

buffer, such as TBS or PBS, and introduced onto one side of a tissue barrier, *e.g.*, injected into the duodenum, jejunum, ileum, colon or other *in vivo* animal site using, for instance, a closed loop model or open loop model. Following injection, samples of bodily fluids located across the tissue barrier, *e.g.*, samples of the portal circulation and/or systemic circulation, were withdrawn at predetermined time points, such as 0 to 90 minutes and/or 2 to 6 hours or more. An aliquot of the withdrawn sample (*e.g.*, blood) was used to directly infect a host, *e.g.*, *E. coli*, in order to confirm the presence of phage. The remaining sample was incubated, *e.g.*, overnight incubation with *E. coli* at 37°C with shaking. The amplified phage present in the culture can be sequenced individually to determine the identity of peptides coded by the phage or, if further enrichment is desired, can be precipitated using PEG, and resuspended in PBS. The phage can then be further precipitated using PEG or used directly for administration to another animal using a closed or open GIT loop model system. Portal or systemic blood samples are collected and the phage transported into such circulation systems is subsequently amplified. In this manner, administration of the phage display library with, if desired, repeat administration of the amplified phage to the GIT of the animal, permitted the selection of phage which was transported from the GIT to the portal and/or systemic circulation of the animal.

If desired, following administration of the phage display library to the tissue barrier (*e.g.*, GIT) of the animal model, the corresponding region of the tissue barrier can be recovered at the end of the procedures given above. This recovered tissue can be washed repeatedly in suitable buffers, *e.g.*, PBS containing protease inhibitors and homogenized in, for example, PBS containing protease inhibitors. The homogenate can be used to infect a host, such as *E. coli*, thus permitting amplification of phages which bind tightly to the tissue barrier (*e.g.*, intestinal tissue). Alternatively, the recovered tissue can be

homogenized in suitable PBS buffers, washed repeatedly and the phage present in the final tissue homogenate can be amplified in *E. coli*. This approach permits amplification (and subsequent identification of the associated peptides) of phages which either bind tightly to the tissue barrier (*e.g.*, intestinal tissue) or which are internalized by the cells of the tissue barrier (*e.g.*, epithelial cells of the intestinal tissue). This selection approach of phage which bind to tissues or which are internalized by tissues can be repeated.

Treatment of animal tissue barriers
***in vivo* with phage display populations**

The purified phage display library (random or preselected) was diluted to 500 μl in PBS buffer and injected into the closed (or open) intestinal loop model (*e.g.*, rat, rabbit or other species). At time 0 and at successive time points after injection, a sample of either the portal circulation or systemic circulation was withdrawn. An aliquot of the withdrawn blood was incubated with *E. coli*, followed by plating for phage plaques or for transduction units or for colonies where the phage codes for resistance to antibiotics such as tetracycline. The remainder of the withdrawn blood sample (up to 150 μl) was incubated with 250 μl of *E. coli* and 5 ml of LB medium or other suitable growth medium. The *E. coli* cultures were incubated overnight by incubation at 37°C on a shaking platform. Blood samples taken at other time points (such as 15 min, 30 min, 45 min, 60 min, up to 6 hours) were processed in a similar manner, permitting amplification of phages present in the portal or systemic circulation in *E. coli* at these times. Following amplification, the amplified phage was recovered by PEG precipitation and resuspended in PBS buffer or TBS buffer. The titer of the amplified phage, before and after PEG precipitation, was determined. The amplified, PEG precipitated phage was diluted to a known phage titer (generally between 10^8 and 10^{10} phage or plaque forming units (p.f.u.) per ml) and was injected into the GIT of the animal

closed (or open) loop model. Blood samples were collected from portal and/or systemic circulation at various time points and the phage transported into the blood samples were amplified in *E. coli* as given above for the first cycle. Subsequently, the phage was PEG-precipitated, resuspended, titered, diluted and injected into the GIT of the animal closed (or open) loop model. This procedure of phage injection followed by collection of portal and/or systemic blood samples and amplification of phage transported into these blood samples can be repeated, for example, up to 10 times, to permit the selection of phages which are preferentially transported from the GIT into the portal and/or systemic circulation.

6.7. Transport of Phage From Rat Lumen Into the Portal and Systemic Circulation

Phage from random phage display libraries as well as control phage were injected into the lumen of the rat gastro-intestinal tract (*in situ* rat closed loop model). Blood was collected over time from either the systemic circulation or portal circulation and the number of phage which were transported to the circulation was determined by titering blood samples in *E. coli*.

The phage display libraries used in this study were D38 and DC43 in which gene III codes for random 38-mer and 43-mer peptides, respectively. As a negative control, the identical phage M13mp18, in which gene III does not code for a "random" peptide sequence, was used. Both the library phages D38 and DC43 were prepared from *E. coli*, mixed together, dialyzed against PBS, precipitated using PEG/NaCl and were resuspended in PBS buffer. The M13mp18 control was processed in a similar manner. The titer of each phage sample was determined and the phage samples were diluted in PBS to approximately the same titers prior to injection into the rat closed loop model.

For sampling from the systemic circulation, approximately 15 cm of the duodenum of Wistar rats was tied

off (closed loop model), approximately 0.5ml of phage solution was injected into the closed loop and blood (0.4ml) was sampled from the tail vein at various times. The time points used (in min) were: 0, 15, 30, 45, 60, 90, 120, 180, 240 and 300 minutes. For sampling from the portal circulation, the portal vein was catheterized, approximately 15 cm of the duodenum was tied off (closed loop model), 0.5ml of phage solution was injected into the closed loop and blood was sampled from the portal vein catheter at various times. As the portal sampling is delicate, sampling times were restricted to 15, 30, 45 and 60 minutes, where possible. The volume of phage injected into each animal was as follows:

Animals (15)	Volume of Phage Injected
R1-R3	0.50 ml
R4	0.43 ml
R5-R15	0.45 ml

The estimated number of transported phage has been adjusted to account for differences in volume injected into each animal (using 0.5 ml as the standard volume).

To investigate transport into the systemic circulation, animals R1, R2 and R3 received the control phage M13mp18 and animals R4, R5, R6 and R7 received the test phage D38/DC43 mix. To investigate transport into the portal circulation, animals R8, R9 and R10 received the control phage M13mp18 and animals R11, R12, R13 and R14 received the test phage D38/DC43 mix. Animal R15* received the combined phage samples from animals R4-R7 (see Table 11) which were sampled from the systemic circulation on day one, followed by amplification in *E. coli*, PEG precipitation and resuspension in PBS. On subsequent analysis, the titer of this phage was found to be 100 times greater than the other phage samples used for animals R8-R14. Thus, the data presented for animal R15* is adjusted down.

Approximately 0.4 ml of the blood was collected at each time point in each model system. 30 μl of the collected blood (systemic) was mixed with 100 μl of the prepared *E. coli* strain K91Kan, incubated at 37°C for 30 min, and plated out for plaque formation using Top Agarose on LB plates. Various negative controls were included in the titering experiments. The following day, the number of plaque forming units was determined. Similarly, 30 μl of the collected blood (portal) and serial dilutions (1:100, 1:1000) thereof was mixed with 100 μl of the prepared *E. coli* strain K91Kan, incubated at 37°C for 30 min, and plated out for plaque formation using Top Agarose on LB plates. The following day, the number of plaque forming units was determined.

In addition, approximately 300 μl of the collected blood from each time point (systemic and portal) was incubated with 5ml of prepared *E. coli* strain K91Kan in modified growth media containing 5mM $MgCl_2$/MgSO4 at 37°C overnight with shaking (to permit phage amplification). The samples were centrifuged and the cell pellet was discarded. Samples of the phage supernatant were collected, serially diluted (10^{-2}, 10^{-4}, 10^{-6}, 10^{-8}) in TBS buffer, and plated for plaques in order to determine the number of plaque forming units present in the amplified phage samples.

Furthermore, an aliquot of phage was removed from the "amplified" supernatants obtained from test animals R4-R7 (samples from each time point were used), combined, and precipitated using PEG for two hours. The precipitated phage was resuspended in PBS buffer and was injected into closed loop model of animal R15*, followed by portal sampling.

The number of phage transported from the closed loop model into the systemic circulation is presented in Table 11 hereafter. The number of phage transported from the closed loop model into the portal circulation is presented in Table 12 hereafter. These numbers are corrected for phage input difference and for volume input differences. Clearly, more phage are present in the portal samples than in the

systemic samples, indicative of either hepatic or RES clearance and/or phage instability in the systemic circulation. In addition, the uptake of phage from the GIT into the portal circulation is quite rapid, with substantial number of phages detected within 15 minutes. The results from the portal sampling experiments would also indicate that the kinetics of uptake of phage from the D38/DC43 libraries is quicker than that of the control phage. Thus, there may be preferential uptake of phage coding for random peptide sequences from the GIT into the portal circulation. In the case of animals R13, R14 and R15*, the % of the phage transported into the titered blood sample within the limited time frame (30, 45 and 15 mins, respectively) was estimated as 0.13%, 1.1% and 0.013%, respectively.

TABLE 11

NUMBER OF PHAGE TRANSPORTED FROM THE CLOSED LOOP MODEL INTO THE SYSTEMIC CIRCULATION

Time (min)	R1	R2	R3	R4	R5	R6	R7
0	0	0	0	0	0	0	0
15	0	1	9	0	0	1	7
30	2	1	0	0	46	1	11
45	10	4	2	1	32	0	20
60	63	19	21	1	114	0	21
90	104	20	18	3	115	0	22
120	94	24	27	0	64	0	6
180	94	12	23	1	413	0	0
240	14	1	20	0	36	0	0
300	1	1	4	2	0	0	0
Total number of transported phage	382	83	124	8	820	2	87

Animals R1, R2 and R3 received the control phage M13mp18.

Animals R4, R5, R6 and R7 received the test phage D38/DC43 mix.

Table 12

NUMBER OF PHAGE TRANSPORTED FROM THE CLOSED LOOP MODEL INTO THE PORTAL CIRCULATION

Time (min)	R8	R9	R10	R11	R12	R13	R14	R15*
15	15	6	3	1	19	231,000	1,000,000	20,000
30	1	5	26	-	0	60,000	272,000	-
45	-	1	555	-	1	-	1,240,000	-
60	-	-	-	-	420,000	-	-	-

Animals R8, R9 and R10 received the control phage M13mp18.

Animals R11, R12, R13 and R14 received the test phage D38/DC43 mix.

Animal R15* received the combined phage samples from animals R4-R7 (see Table 11) which were sampled from the systemic circulation on day one, followed by PEG precipitation and resuspension in PBS. On subsequent analysis, the titer of this phage was found to be 100 times greater than the other phage samples used for animals R8-R14. Thus, the data measuring phage transport into the portal circulation for animal R15* is adjusted down.

These studies demonstrated that both the control phage and the D38/DC43 phages are transported over time from the lumen of the GIT into the portal and systemic circulation, as demonstrated by titering the phage transported to the blood in *E. coli*. More phage were transported from the test phage samples into the portal circulation than the corresponding control phage sample. In addition, the kinetics of transport of the test phage into the portal circulation appeared to exceed that of the control phage. Phage from the D38/DC43 libraries which appeared in the systemic circulation of different animals (R4-R7) were pooled, amplified in *E. coli*, precipitated, and re-applied to the lumen of the GIT, followed by collection in the portal circulation and titering in *E. coli*. These selected phage were also transported from the lumen of the GIT into the portal circulation. This *in situ* loop model may represent an

attractive screening model in which to identify peptide sequences which facilitate transport of phage and particles from the GIT into the circulation.

Using this screening model system, a number of preselected phage libraries now exist, including a one pass systemic phage library from animals R4-R7, a one-pass portal library from animals R11-R14, and a two pass, rapid transport, systemic-portal phage library SP-2 from animal R15*.

6.8. Transport of Phage From Preselected Phage Libraries From the Rat Lumen Into the Portal and Systemic Circulation

Four preselected phage libraries, GI-D2H, GI-hSI, GI-HPT1 and GI-hPEPT1, were constructed by pooling phage previously selected by screening random phage display libraries D38 and DC43 using the HPT1, HPEPT1, D2H and hSI receptor or binding sites located in the GIT. The phage pools, preselected phage libraries are shown in Table 13. Note that the sequences for PAX2, HAX1, HAX5, HAX6, HAX10, H10 and HAX44 are the same. Also, the sequence for HAX40 is the same as that for H44. The corresponding SEQ ID NOS. are shown in Table 7.

Table 13

PRESELECTED PHAGE LIBRARIES

D2H	HSI	HPT1	hPEPT1
DAB3	S15	HAX9	PAX2 (H10)
DAB7	S21	HAX35	PAX9
DAB10	S22	HAX40 (H44)	PAX14
DAB18	SNi10	HAX42	PAX15
DAB24	SNi28	HCA3	PAX16
DAB30	SNi34	HAX1	PAX17
DAX15	SNi38	HAX5	PAX18
DAX23	SNi45	HAX6	PAX35
DAX24	SNiAX2	HAX10	PAX38
DAX27	SNiAX6	H40	PAX40
DCX8	SNiAX8	M13mp18	PAX43
DCX11	M13mp18		PAX45
DCX26			PAX46
DCX33			P31
DCX36			P90

DCX39	5PAX3
DCX42	5PAX5
DCX45	5PAX7
M13mp18	5PAX12
	H40
	M13mp18

Similar to methods described herein above, these preselected phage libraries together with the negative control phage M13mp18 were injected into the rat closed loop model (6 animals per preselected phage library), blood was collected over time from the portal circulation via the portal vein and, at the termination of the experiment, a systemic blood sample was collected from the tail vein and the intestinal tissue region from the closed loop was collected.

In particular, phages selected *in vitro* to each receptor or binding site located in the GIT were amplified in *E. coli*, PEG-precipitated, resuspended in TBS and the titer of each phage sample was determined by plaquing in *E. coli* as described above. Subsequently, an equal number of each phage (8×10^8 phage) for each receptor site was pooled into a preselected phage library together with the negative control phage M13mp18 and each preselected phage library was administered to 6 Wistar rats per library (rats 1-6; GI-D2H, rats 7-12; GI-hSI, rats 13-18; GI-hPEPT1, and rats 19-24; GI-HPT1). Using the *in situ* loop model described above, 0.5 ml of preselected phage library solution was injected into the tied-off portion of the duodenum/jejunum. Blood was collected into heparinized tubes from the portal vein at 0, 15, 30, 45 and 60 minutes. A blood sample was taken from the systemic circulation at the end of the experiment. Similarly, the portion of the duodenum/jejunum used for phage injection was taken at the end of the experiment.

Thirty microliters of the collected portal blood (neat and 10^{-2}, 10^{-4}, 10^{-6} dilutions) was added to 30 μl *E. coli* K91Kan cells (overnight culture) and incubated at 37°C for 10 min. Subsequently, 3 ml of top agarose was added and the samples were plated for plaques. One hundred microliters of

the collected portal blood was added to 100μl of *E. coli* K91Kan. Five milliliters of LB medium was then added and the samples were incubated at 37°C overnight in a rotating microbial incubator. The *E. coli* was removed by centrifugation and the amplified phage supernatant samples were either titered directly or were PEG-precipitated, resuspended in TBS and titered. Following titration of the amplified phage, samples containing phage from each set of animals were combined, adjusting the titer of each sample to the same titer, and were plated for plaques on LB agar plates (22cm^2 square plates). Either 12,000 or 24,000 phage were plated for plaques.

Thirty microliters of the collected systemic blood (neat and 10^{-2}, 10^{-4}, 10^{-6} dilutions) was added to *E. coli* K91Kan cells, incubated at 37°C for 10 min. Three ml of top agarose was then added and the samples were plated for plaques. One hundred microliters of the collected systemic blood was added to 100μl of *E. coli* K91Kan, incubated at 37°C for 10 min. Five milliliters of LB medium was then added and the samples were incubated at 37°C overnight in a rotating microbial incubator. The *E. coli* was removed by centrifugation and the amplified phage supernatant samples were either titered directly or were PEG-precipitated, resuspended in TBS and titered. Following titration of the amplified phage, samples containing phage from each set of animals were combined, adjusting the titer of each sample to the same titer, and were plated for plaques on LB agar plates (22cm^2 square plates). Either 12,000 or 24,000 phage were plated for plaques.

The intestinal tissue portion used in each closed loop was excised. The tissue was cut into small segments, followed by 3 washings in sterile PBS containing protease inhibitors, and homogenized in an Ultra thorex homogeniser (Int-D samples). Alternatively, the tissue (in PBS supplemented with protease inhibitors) was homogenized in an Ultra Thorex homogenizer, washed 3 times in PBS containing protease inhibitors and resuspended in PBS containing

protease inhibitors (Int-G samples). In each case, serial dilutions (neat and 10^{-2}, 10^{-4}, 10^{-6} dilutions) of the tissue homogenate was titered in *E. coli*. In addition, an aliquot (100μl) of the tissue homogenate was added to 100μl of *E. coli* K91Kan, incubated at 37°C for 10 min, followed by addition of 5ml of LB medium and incubation overnight at 37°C in a rotating microbial incubator.

The phage amplified from the portal blood, systemic blood and intestinal tissue was plated for plaques. The plaques were transferred to Hybond-N Nylon filters, followed by denaturation (1.5M NaCl, 0.5M NaOH), neutralization (0.5M TRIS-HCl, pH7.4, 1.5M NaCl), and washing in 2X SSC buffer. The filters were air-dried, and the DNA was cross-linked to the filter (UV crosslinking: 2min, high setting). The filters were incubated in pre-hybridization buffer (6X SSC, 5X Denhardt's solution, 0.1% SDS, 20μg/ml yeast tRNA) at 40°C-45°C for at least 60 min.

Synthetic oligonucleotides, (22-mers), complimentary to regions coding for the receptor or binding sites used to create the preselected phage library, were synthesized (see Table 14 below).

Table 14

OLIGONUCLEOTIDES USED IN *IN VIVO* SCREEN

CLONE NAME	OLIGO	SEQ. ID. NO.
S15	5'TCCGGACTCTCATAAGCGCCGG3'	111
S21	5'ACAACGGGCCAGAAAGAGCGAG3'	112
S22	5'ACACCACCCCAATCGGAGCTAC3'	113
SNi10	5'TCAGAATCCGTGCACTGGCCAA3'	114
SNi28	5'GCCCTATTCATACCACCGGAGT3'	115
SNi34	5'CATCAGTCCTACCGCCGAAAAG3'	116
SNi38	5'CGTATAGCTATTGTGAGCGATG3'	117
SNi45	5'ACGCGCGGAACGAGCAGTACCA3'	118
SNiAX2	5'CCATAATGATCCCCGTCACTAT3'	119
SNiAX6	5'AGACACCCCTTAGCCGTCGTAG3'	120
SNiAX8	5'AGCTCCGTGACCTTAGTCATAA3'	121

CLONE NAME	OLIGO	SEQ. ID. NO.
DAB3	5'TGCACAGCTCAGCGCCGCACCA 3'	122
DAB7	5'ACGGGTCATCAGCGCCGCACCA 3'	123
DAB10	5'TGTCACCCCCCTCCCCGGACTT 3'	124
DAB18	5'ACTCGCAATTATTGGCGCTCGA 3'	125
DAB24	5'GTCTTCTCAACCTTATCCTGCG 3'	126
DAB30	5'AAAGCCCCCTGCTAAACTCCCA 3'	127
DAX15	5'CTGCGTCTGCCACGTCGTCATC 3'	128
DAX23	5'GTTAAAAGAGGGCAAGCTCGGA 3'	129
DAX24	5'CCGAGTTCTTGATGTCCTCCAT 3'	130
DAX27	5'TCCAATGCCTGTACCACGGATG 3'	131
DCX8	5'TCGCAACCGATATCGTGCTTAT3'	132
DCX11	5'TGCATACACTGCTTGGAGCCCT3'	133
DCX26	5'GAAATCTCACTAGTAGTCCGCC3'	134
DCX33	5'GCGGGCAAGACAGTCCAATTCC3'	135
DCX36	5'GAGCTCCAATTCCACGACGACC3'	136
DCX39	5'GGTTGCCATGCGTTCAAACTAC3'	137
DCX42	5'TCCCGCGGGGACAAACCCGAAT3'	138
DCX45	5'CTGCTAGTCTTATCATTCCCCA3'	139
PAX2	5'CTATCGACACTATAGGGCCTAC3'	140
PAX9	5'TACCCTTGTAACCCACACTAGG3'	141
PAX14	5'TTCTTCTGAATAGACCGGCCGA3'	142
PAX15	5'CCACCACCCTTAACCCGACAAT3'	143
PAX16	5'AGGGGGAGACTTGTTCACAAAC3'	144
PAX17	5'CGGCTCATACCACCGAAAGCTA3'	145
PAX18	5'ATCGTCCTACTGTAATCCTCGA3'	146
PAX35	5'GACACACTACTCAGGTCCACCT3'	147
PAX38	5'CCATAATCAACATTGCCGCCCT3'	148
PAX40	5'CAAAACGCTCGCCCCAAACTCA3'	149
PAX43	5'GTAAACTTGTGCTTCTCGCACC3'	150
PAX45	5'CCATGGTCCGGGTACACCTGAA3'	151
PAX46	5'GTTACTAACGGAACGAGACCTA3'	152
P31	5'TGTTGGCGTTCTCAACCCCGTT3'	153
P90	5'ACAACCGGAGTTGTTCTGCCTA3'	154
5PAX3	5'TAAGCATCGGCCACGTTCTTCG3'	155
5PAX5	5'TTATCCCTGGTGTGCAGGTTGA3'	156

CLONE NAME	OLIGO	SEQ. ID. NO.
5PAX7	5'TATCAGAATCGTAGTCGGACGG3'	157
5PAX12	5'CTTTGTAATGGAACCACAACCC3'	158
HAX9	5'CGGTGGCTCATCTCCCTCTTAT3'	159
HAX35	5'ATCAGACTGGCTGGGACCACAA3'	160
HAX40	5'CACAACCTCCTCTCCGCGAACT3'	161
HAX42	5'AGATTCGTCCCCAACGCGTGAT3'	162
HCA3	5'GGGAATTCGCAAAGCTATACTC3'	163
H40	5'CCCCGTGGAATTCAACCTGTGA3'	164
M13 (positive)	5'GTCGTCTTTCCAGACGT3'	165
M13 (negative)	5'CTTGCATGCCTGCAGGTCGAC3'	166

The oligonucleotides (5pmol) were 5'end labelled with ^{32}P-ATP and T4 polynucleotide kinase and approximately 2.5pmol of labelled oligonucleotide was used in hybridization studies. Hybridizations were performed at 40-45°C overnight in buffer containing 6X SSC, 5X Denhardt's solution, 0.1% SDS, 20μg/ml yeast tRNA and the radiolabeled synthetic oligonucleotide, followed by washings (20-30 min at 40-45°C) in the following buffers: (i) 2X SSC / 0.1% SDS, (ii) 1X SSC / 0.1% SDS, (iii) 0.1X SSC / 0.1% SDS. The filters were air-dried and exposed for autoradiography for 15 hours, 24 hours or 72 hours.

Hybridization data indicated that all the oligonucleotide probes bound specifically to their phage target except for the HAX9 probe which apparently was not labeled. A negative control probe that hybridized only to M13mp18 DNA showed a weak to negative signal in all samples tested (data not shown).

Hybridization data for pools from each receptor group of rats was compiled. Tables 15, 16, 17 and 18 show a representative compilation of autoradiograph signals of the HSI, D2H, HPT1 and hPEPT1 receptor groups. These Tables show the phage absorption and uptake from the closed loop GIT model to portal and systemic circulation and phage absorption/internalization to intestinal tissue. In these Tables, Int-G refers to intestinal tissue homogenized prior

to washing and recovery while Int-D refers to intestinal tissue washed prior to homogenization and phage recovery. In all cases, leading phage candidates were present in more than one animal.

Table 15

SUMMARY OF AUTORADIOGRAPH SIGNALS OF HSI ANIMAL STUDY

Phage	Portal	Int.-G	Int.-D
S15	++	+/-	+/-
S21	-	-	-
S22	-	-/+	-
SNi-10	+++/+	++	++
SNi-28	-	-	-
SNi-34	++	-	-
SNi-38	++	-	-
SNi-45	-	-	-
SNiAX-2	-	-	-
SNiAX-6	-	-	-
SNiAX-8	-	-	-
M13	++++++	++++++	++++++
M13	nd*	+	-

*not detected

Table 16

SUMMARY OF AUTORADIOGRAPH SIGNALS OF D2H ANIMAL STUDY

Phage	Portal	Int.-G	Int.-D
DAB3	+++	+/-	-/+
DAB7	++	++	-/+
DAB10	++++++	+/-	-/+
DAB18	-	-	-
DAB24	-	-	-
DAB30	++++	++	+++
DAX15	-	-	-
DAX23	-/+	+	-/+
DAX24	-	-	-
DAX27	-	+	-
DCX8	+++++	+/-	-
DCX11	++++++	++	-/+
DCX26	-	-	-
DCX33	+++	++	++
DCX36	-	-	-
DCX39	-	-/+	-
DCX42	-	-	-/+
DCX45	-	++	-
M13 (+)	+++++	+++++	+++++
M13 (-)	+/-	-/+	-

Table 17

SUMMARY OF AUTORADIOGRAPH SIGNALS OF HPT1 ANIMAL STUDY

Phage	Int.-G	Portal	Systemic
H40	-	-	++++
HAX9	ND	ND	ND
HAX35	-	+	-
HAX40	-	-	-
HAX42	-	++	++
HCA3	-	-	-
PAX2	-	+++	++++
M13(+)	++++++	++++++	++++++
M13(-)	-	--/+	-

Table 18

SUMMARY OF AUTORADIOGRAPH SIGNALS OF hPEPT1 ANIMAL STUDY

Phage	Int.-G	Portal	Systemic
PAX2	-	++	-
PAX9	++	+++	-
PAX14	-	++	-
PAX15	-/+	-	-
PAX16	-	-	-
PAX17	+	++/+	-
PAX18	-	-	-
PAX35	-	-	-
PAX38	-/+	-	-
PAX40	+	+++	-
PAX43	+	-	-
PAX45	-	-	-
PAX46	-	+++	-
P31	++	++++	++
5PAX3	++/+	++	-
5PAX5	-	-	++
5PAX7	+++	-	-
5PAX12	++++	++	-
H40	++	++	-
M13(+)	++++++	++++++	++++++
M13(-)	-	-	-

Apart from the synthetic oligonucleotide to HAX9, all oligonucleotides were initially confirmed to be radiolabeled, as determined by hybridization to the corresponding phage target (eg., phage S15 hybridized to the oligonucleotide S15). In addition, under the experimental conditions used, the oligonucleotides essentially did not hybridize to the negative control phage template M13mp18. Two oligonucleotides were synthesized to the phage M13mp18: (1) a positive oligonucleotide which hybridizes to a conserved sequence in both M13mp18 and each of the GIT receptor or GIT binding site selected phages [designated M13 (positive)]; and (2) a negative oligonucleotide which only hybridizes to a sequence unique to the multiple cloning site of phage M13mp18 and which does not hybridize to any of the GIT receptor or GIT binding site selected phages.

In the case of the hSI pool of phages, only four phages were transported from the closed loop model into the portal circulation: phages S15, SNi-10, SNi-34 and SNi-38. The other phages, S21, S22, SNi-28, SNi-45, SNiAX-2, SNiAX-6 and SNiAX-8, were not transported from the GIT into the portal circulation. In addition, phages SNi-10 and to a lesser extent phages S15 and S22 were found in the intestine samples or fractions, whereas the other phages were not. There was a very low presence (<0.1%) of the phage M13mp18 in the Int-G samples. These results show that phages can be further selected from pre-selected libraries, permitting the identification of phages which are transported from the GIT closed loop into the portal circulation or phages which bind to or are internalized by intestinal tissue.

In the case of the D2H pool of phages, there was a rank order by which phages were transported from the GIT closed loop model into the portal circulation, with phages DCX11 and DAB10 preferably transported, followed by phages DCX8, DAB30, DAB3 and DAB7. A number of phages from this pool were not transported into the portal circulation, including phages DAB18, DAB24, DAX15, DAX24, DAX27, DCX26, DCX36, DCX39, DCX42, DCX45. There is a very low level of transport of phage DAX23 from the GIT into the portal circulation. Similarly, only some of the phages were found in the intestinal samples fractions, including phages DAB30, DCX33, DAB7, DCX11, DCX45 and to a much lesser extent phages DAB3, DAB10, DCX8, DCX39, DCX42. Some phages were not found in the intestinal samples, including phages DAB18, DAB24, DAX15, DAX24, DCX26, and DCX36. There was a very low presence (<0.1%) of the phage M13mp18 in the Int-G samples. These results showed that phages can be further selected from pre-selected libraries, permitting the identification of phages which are transported from the GIT closed loop into the portal circulation or phages which bind to or are internalized by intestinal tissue.

In the case of the HPT1 pool of phages, there was a rank order by which phages were transported from the GIT closed

loop model into the portal or systemic circulation. Phage PAX2 (which was used at a 4X concentration relative to the other phages in this pool) followed by phage HAX42 was found in the portal and systemic circulation; phage H40 was found in the systemic circulation only. None of the phages in this pool were found in the intestine samples or fractions. Phage M13mp18 was not found in the intestine fractions or systemic circulation, with very low incidence (<0.001%) in the portal circulation. These results show that phages can be further selected from pre-selected libraries, permitting the identification of phages which are transported from the GIT closed loop into the portal and/or systemic circulation or phages which bind to or are internalized by intestinal tissue.

In the case of the hPEPT1 pool of phages, the phages PAX2 and H40 were also included in this pool. A number of phages from this pool were found in the portal circulation, including phages P31 (SEQ ID NO:43), PAX46, PAX9, H40, PAX17, PAX40, PAX2, PAX14, 5PAX3 and 5PAX12. A number of phages were not found in the portal blood including the negative control phage M13mp18, PAX15, PAX16, PAX18, PAX35, PAX38, PAX43, PAX45, P90, 5PAX5 and 5PAX7. The only phage found in the systemic circulation were phages 5PAX5 and P31 (SEQ ID NO:43). In addition, there was preferential binding of some phages to the intestine, including phages 5PAX12, 5PAX7, 5PAX3, H40, P31 (SEQ ID NO:43), PAX9, and to a lesser extent phages PAX38 and PAX15. Some phages were not found in the intestine samples, including the negative control phage M13mp18 and the phages PAX2, PAX14, PAX16, PAX18, PAX35, PAX45, PAX46, P90 and 5PAX5. These results show that phages can be further selected from pre-selected libraries, permitting the identification of phages which are transported from the GIT closed loop into the portal and/or systemic circulation or phages which bind to or are internalized by intestinal tissue.

Further Characterization of Select Sequences

Following initial screening of the four recombinant receptor sites (hPEPT1, HPT1, D2H, hSI) of the gastrointestinal tissue, with the phage display libraries, a series of phage were isolated which showed preferential binding to the respective target receptor sites in comparison to negative control protein BSA protein and the recombinant protein recombinant human tissue factor (hTF) (which, like the recombinant receptors of the gastrointestinal tissue, contained a poly-histidine tag at its NH_2-terminal end). In subsequent experiments same titers of the selected phage which bound to each target receptor site were combined into a single pool (*i.e.*, one pool of HPT1 binding phage, one pool of hPEPT1 binding phage, one pool of D2H binding phage, and one pool of hSI binding phage). Each pool was supplemented with an equivalent titer of the negative control phage M13mp18. These phage pools were injected into a closed duodenal loop region of rat intestinal tissue and subsequently phage was harvested and recovered which was bound to and retained by the intestinal tissue and/or was absorbed from the intestinal loop into the portal and/or systemic circulation. In addition, a selection of the initial phages which bound to the target recombinant receptor site were analyzed for binding to either fixed Caco-2 cells and/or to fixed C2BBe1 cells. The selection of the final lead peptide sequences was based on the ability of the phage, coding for that peptide sequence (1) to bind to the target recombinant receptor site *in vitro* in preference to its binding to the negative control proteins BSA and/or hTFs, (2) to bind to rat intestinal tissue following injection into a closed duodenal loop of rat intestinal tissue in preference to the negative control phage M13mp18, (3) to be absorbed from rat intestinal tissue into either the portal and/or systemic circulation following injection into a closed duodenal loop of rat intestinal tissue in preference to the negative control phage M13mp18, and (4) to bind to either fixed Caco-2 cells or fixed C2BBe1 cells in phage binding

studies in preference to the negative control phage M13mp18. Peptides were also selected with consideration to the ease of chemical synthesis.

6.9. GST Fusion Proteins of GIT Targeting Peptides Construction of GST Fusion Proteins of GI Targeting Peptides

Glutathione S-transferase (GST) vectors encoding fusion proteins of GI targeting peptides were constructed in the vector pGEX4T-2 (source, Pharmacia Biotech, Piscataway, NJ). Briefly, single-strand DNA from the clones of interest were amplified by the polymerase chain reaction. The amplified DNA was then cleaved with the restriction enzymes XhoI and NotI and then ligated into SalI/NotI cleaved pGEX4T-2. Following transformation, the DNA sequence for each construct was verified by sequencing.

For construction of the truncated versions of the GST fusion proteins, where the inserted sequence was less than 45 base pairs, overlapping oligonucleotides containing cohesive SalI and NotI termini, and encoding the sequence of interest, were annealed and then ligated directly into SalI/NotI cleaved pGEX4T-2. Following transformation, the DNA sequence for each construct was verified.

A diagrammatic representation of the various GST fusion protein constructs that have been synthesized is indicated in Figures 5A-5C.

Expression and Purification of GST Fusion Proteins

Escherichia coli BL21 cells containing GST fusion protein constructs were grown overnight in 2X YT media containing 100 μg/ml ampicillin (2X YT/amp). Overnight cultures were diluted 1:100 in 2X YT broth (100 ml), and cells were grown to an A_{600} of 0.5 at 30°C, induced with 1mM isopropyl-1-thio-B-D-galactopyranoside, and grown for an additional 3 h. Cells were harvested by centrifugation and resuspended in 5 ml of PBS containing a mixture of the proteinase inhibitors (Boehringer/Mannheim). Cells were

sonicated on ice, and the cell lysates were centrifuged at 12,000 x g for 10 minutes at 4°C. Supernatant fractions were reacted for 30 minutes at room temperature with 2 ml of a 50% slurry of glutathione-Sepharose® 4B, washed 3 times with 1.5 ml of PBS (at room temperature), and the bound GST fusion proteins were eluted by reaction for 10 minutes at room temperature with 3 X 1ml of 10 mM reduced glutathionein 50 mM Tris HCl pH 8.0. Protein was quantified by the Bio-Rad protein assay followed by characterization by SDS-polyacrylamide gel electrophoresis.

ELISA of GST fusion peptides

The standard ELISA procedure was modified as follows. GST proteins were diluted to an appropriate concentration in PBS containing 1%BSA and 0.05% Tween20 (1%BPT), titered and incubated one hour at room temperature. Following five washes an anti-GST monoclonal antibody was added (Sigma, St. Louis Clone GST-2 diluted 1:10,000 in 1%BPT) and incubated one hour. After five more washes goat anti-mouse IgG2b-HRP was added (Southern Biotechnology Associates Inc., Birmingham, AL, diluted 1:4000 in 1%BPT) and incubated one hour. After five washes plates were developed with TMB peroxidase substrate (Kirkegard and Perry, Gaithersburg, MD). All data is presented with background binding subtracted.

Figure 6 shows the binding of GST-SNi10, GST-SNi34 and GST alone to the hSI receptor and to fixed C2BBe1 cells.

GST Fusion Proteins of Selected GIT Targeting Peptides

Results show that GST-DXB8, GST-PAX2, GST-P31, GST-SNi10 and GST-SNi34 bound fixed Caco-2 or C2BBe1 cells (Figures 7 and 8) relative to GST control binding. GST-HAX42, GST-5PAX5, all showed weak to moderate binding relative to GST control.

Interestingly, P31 truncation 103-GST fusion protein bound almost as well as full-length P31 (SEQ ID NO:43) to fixed Caco-2 cells (A). This suggests the portion

of the P31 sequence (SEQ ID NO:43) responsible for binding resides in this portion. PAX2.107 bound similarly to full-length PAX2; therefore, this portion most likely contains the amino acid sequence responsible for binding (B). In preliminary assays, none of the DCX8 truncations bound similarly to full-length DCX8 to Caco-2 cells suggesting the binding region spans more than one of these pieces.

Inhibition of Binding by Synthetic Peptides

Binding of GST-P31 to fixed C2BBe1 Cells

The standard ELISA procedure was modified as follows. GST fusion proteins and peptides were diluted to an appropriate concentration in PBS containing 1% BSA and 0.05% Tween 20. Peptides were titered, a constant concentration of diluted GST protein was added to titered peptides and the mixture was incubated one hour at room temperature. Following five washes, an anti-GST monoclonal antibody was added (Sigma, St. Louis Clone GST-2 diluted 1:10,000 in 1% BPT) and incubated one hour. After five more washes goat anti-mouse IgG2b-HRP was added (Southern Biotechnology Associates Inc., Birmingham, AL, diluted 1:4000 in 1% BPT) and incubated one hour. After five washes plates were developed with TMB peroxidase substrate (Kirkegard and Perry, Gaithersburg, MD). All data is presented with background binding subtracted.

Figures 9A and 9B show the inhibition of GST-P31 binding to C2BBe1 fixed cells. The peptide competitors are ZElan024 which is the dansylated peptide version of P31 (SEQ ID NO:43) and ZElan044, ZElan049 and ZElan050 which are truncated, dansylated pieces of P31 (SEQ ID NO:43). Data is presented as O.D. vs. peptide concentration and as percent inhibition of GST-P31 binding vs. peptide concentration. Uncompeted GST-P31 binding was considered as 100% binding. IC_{50} values are estimates using the 50% line on the percent inhibition graph.

GST-P31 and GST-PAX2 exhibited no crossreactive binding to ZElan024 (P31) (SEQ ID NO:43) and ZElan018 (PAX2)

at the 0.5 $\mu g/ml$ concentration used in competition assays. GST-HAX42 exhibited crossreactivity to ZElan018 (PAX2) and ZElan021 (HAX42) at the 5 $\mu g/ml$ concentration used in competition assays.

Figures 10A-10C present a compilation of data generated by competition ELISA of GST-P31, GST-PAX2, GST-SNi10 and GST-HAX42 versus various dansylated peptides on fixed C2BBe1 cells. IC_{50} values are in μM and include ranges determined from multiple assays. The GST/C2BBe1 column is a summary of GST protein binding to fixed C2BBe1 cells.

Binding to fixed Caco-2 Cells

Caco-2 cells were fixed, treated with phenylhydrazine and blocked as described above. Synthetic peptides (100$\mu g/ml$) were applied in duplicate to Caco-2 cells and serially diluted down the 96-well plate. The corresponding GST-peptide fusion protein (10μg) was added to each well and the plates were incubated for 2h at room temperature with agitation. Binding of the GST-peptide fusion proteins to the cells was assayed using the ELISA technique described above. GST-P31 binding was inhibited by ZElan024, ZElan028 and ZElan031 as well as the two D forms ZElan053 and ZElan054. GST-PAX2 binding was inhibited by ZElan032, ZElan033, and ZElan035. GST-HAX42 binding was not inhibited by ZElan021 (full length HAX42) but it was inhibited by ZElan018 (PAX2) and ZElan026 and ZElan038 (scrambled PAX2 peptides).

Transport and Uptake of GST-Peptide Fusions into Live Caco-2 Cells

Transport and uptake of GST-peptide fusions and deletion derivatives across cultured polarized Caco-2 monolayers over 4 hours in HBSS buffer was examined using an anti-GST ELISA assay. In another experiment, transport and uptake of GST-peptide fusions and deletion derivatives across

cultured polarized Caco-2 monolayers over 24 hours in serum-free medium (SFM) was examined using an anti-GST ELISA assay.

Materials

Buffered Hank's balanced salt solution (bHBSS) = 1x HBSS (Gibco CN.14065-031) supplemented with 0.011M glucose (1g/l), 25 mM Hepes (15 mM acid (3.575g/l; Sigma CN.H3375); 10mM base (2.603g/l; Sigma CN.H1016)].

Chloroquine: Made up as 10mM solution in water [Sigma CN C6628]

Lysate buffer: 30 mM Tris-HCl pH8.0; 1mM EDTA

Serum-free medium (SFM) is normal medium without serum.

Method

a) 4h HBSS study: Transepithelial electrical flux (TER) across the Caco-2 monolayers grown on snapwells (passage 33; 23 days old) was measured to confirm monolayer integrity before beginning the experiment. The medium was removed and the cells were washed once with bHBSS. bHBSS containing 100μM chloroquine was added and the cells were incubated for 2h at 37°C. The bHBSS+chloroquine was replaced with 0.5ml bHBSS containing GST-peptide fusions (100μg/ml) and the cells were incubated as before. Basolateral samples were removed at the following times: 0, 0.5h, 2h, and 4h. At 4h, TER was measured, the apical medium was sampled and the apical reservoir was washed 6 times with HBSS. The cells were allowed to lyse for 1h on ice in lysate buffer, after which, lysate sample was collected. All samples were stored at -70°C until assay by anti-GST ELISA. Before analysis, samples were normalized for protein content relative to each other using a BioRad protein assay.

b) 24h SFM study: Transepithelial electrical flux (TER) across the Caco-2 monolayers grown on snapwells (passage 33; 23 days old) was measured to confirm monolayer integrity before beginning the experiment. The medium was removed and the cells were washed once with SFM. SFM

containing GST-peptide fusions (100μg/ml) was added to the cells which were incubated at 37°C for 24h at 5% CO2. After 24 hours, TER readings were taken, and samples from the basolateral and apical reservoirs were removed. The apical reservoir was washed 6 times with PBS. The cells were allowed to lyse for 1h on ice in lysate buffer, after which lysate sample was collected. All samples were stored at -70° until assay by anti-GST ELISA. Before analysis, samples were normalized for protein content relative to each other using a BioRad protein assay.

Results

All of the GST-peptide fusions and controls examined were transported across live Caco-2 monolayers. Full-length GST-P31 and GST-DCX8, but not truncations of these molecules had a higher flux than GST alone.

Internalization of GST-peptide fusions into polarized Caco-2 cells was investigated in two experiments. In experiment 1, 15μg of GST-peptide fusion was applied in bHBSS and internalized GST-peptide was recovered by lysing the cells after 4h. In experiment 2, 10μg of GST-peptide was applied in either a) bHBSS (lysate recovered after 4h), or b) serum-free medium (lysate recovered after 24h).

Figure 11A describes complete transport of GST-peptide across a polarized Caco-2 monolayer and does not necessarily refer to internalization, *i.e.*, the GST-peptide was recovered from the basolateral reservoir of a snapwell but the proteins could have crossed the barrier by the paracellular route.

Effect of Thrombin Cleavage on Binding of GST-Peptide Fusions to Fixed Caco-2 Cells

Binding of intact and thrombin-cleaved GST-peptide fusions to fixed Caco-2 cells was compared. Reduced binding of the thrombin-cleaved GST-peptide fusions relative to intact fusions indicates that the peptide component of the fusion, and not the GST domain, mediates binding.

Method

Confluent Caco-2 monolayers grown in 96-well plates (p38) were fixed and treated with 0.1% phenylhydrazine before blocking with 0.1% BSA in PBS. Thirty micrograms of each GST-peptide was treated with bovine thrombin (1μ/ml; 0.4 NIH units; Sigma CN.T9681) for 18h at room temperature in 20mM Tris-HCl pH8.0, 150mM NaCl, 2.5mM $CaCl_2$. Controls were similarly treated without addition of thrombin. Ten micrograms of each GST-peptide fusion was removed for PAGE analysis, and 10μg of fusions were added in duplicate to the fixed Caco-2 cells before 5-fold serial dilutions (1% BPT diluent). The fusions were allowed to bind for 1h at room temperature. Following 6 washes with 1% BPT, binding was assayed by ELISA.

Results

Results are shown in Figure 12.

Conclusions:

PAGE analysis confirmed that the GST-peptide fusions were effectively cleaved with thrombin. Cleavage with thrombin significantly reduced detection of binding of GST-P31.103, GST-PAX2.106, GST-DCX8, GST-SNi10 to fixed Caco-2 cells, indicating that the peptide component, and not the GST domain, mediates binding.

6.10. Synthesis of Peptides

6.10.1. Procedure For Solid Phase Synthesis

Peptides may be prepared by methods that are known in the art. For example, in brief, solid phase peptide synthesis consists of coupling the carboxyl group of the C-terminal amino acid to a resin and successively adding N-alpha protected amino acids. The protecting groups may be any known in the art. Before each new amino acid is added to the growing chain, the protecting group of the previous amino acid added to the chain is removed. The coupling of amino acids to appropriate resins is described by Rivier et al.,

U.S. Patent No. 4,244,946. Such solid phase syntheses have been described, for example, by Merrifield, 1964, J. Am. Chem. Soc. 85:2149; Vale et al., 1981, Science 213:1394-1397; Marki et al., 1981, J. Am. Chem. Soc. 103:3178 and in U.S. Patent Nos. 4,305,872 and 4,316,891. In a preferred aspect, an automated peptide synthesizer is employed.

By way of example but not limitation, peptides can be synthesized on an Applied Biosystems Inc. ("ABI") model 431A automated peptide synthesizer using the "Fastmoc" synthesis protocol supplied by ABI, which uses 2-(1H-Benzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate ("HBTU") (R. Knorr et al., 1989, Tet. Lett., 30:1927) as coupling agent. Syntheses can be carried out on 0.25 mmol of commercially available 4-(2',4'-dimethoxyphenyl-(9-fluorenyl-methoxycarbonyl)-aminomethyl)-phenoxy polystyrene resin ("Rink resin" from Advanced ChemTech) (H. Rink, 1987, Tet. Lett. 28:3787). Fmoc amino acids (1 mmol) are coupled according to the Fastmoc protocol. The following side chain protected Fmoc amino acid derivatives are used: FmocArg(Pmc)OH; FmocAsn(Mbh)OH; FmocAsp(^{t}Bu)OH; FmocCys(Acm)OH; FmocGlu(^{t}Bu)OH; FmocGln(Mbh)OH; FmocHis(Tr)OH; FmocLys(Boc)OH; FmocSer(^{t}Bu)OH; FmocThr(^{t}Bu)OH; FmocTyr(^{t}Bu)OH. [Abbreviations: Acm, acetamidomethyl; Boc, tert-butoxycarbonyl; ^{t}Bu, tert-butyl; Fmoc, 9-fluorenylmethoxycarbonyl; Mbh, 4,4'-dimethoxybenzhydryl; Pmc, 2,2,5,7,8-pentamethylchroman-6-sulfonyl; Tr, trityl].

Synthesis is carried out using N-methylpyrrolidone (NMP) as solvent, with HBTU dissolved in N,N-dimethylformamide (DMF). Deprotection of the Fmoc group is effected using approximately 20% piperidine in NMP. At the end of each synthesis the amount of peptide present is assayed by ultraviolet spectroscopy. A sample of dry peptide resin (about 3-10 mg) is weighed, then 20% piperidine in DMA (10 ml) is added. After 30 min sonication, the UV (ultraviolet) absorbance of the dibenzofulvene-piperidine adduct (formed by cleavage of the N-terminal Fmoc group) is

recorded at 301 nm. Peptide substitution (in mmol g^{-1}) can be calculated according to the equation:

$$\text{substitution} = \frac{A \times v}{7800 \times w} \times 1000$$

where A is the absorbance at 301 nm, v is the volume of 20% piperidine in DMA (in ml), 7800 is the extinction coefficient (in $mol^{-1}dm^3cm^{-1}$) of the dibenzofulvene-piperidine adduct, and w is the weight of the peptide-resin sample (in mg).

Finally, the N-terminal Fmoc group is cleaved using 20% piperidine in DMA, then acetylated using acetic anhydride and pyridine in DMA. The peptide resin is thoroughly washed with DMA, CH_2Cl_2 and finally diethyl ether.

6.10.2. <u>Cleavage and Deprotection</u>

By way of example but not limitation, cleavage and deprotection can be carried out as follows: The air-dried peptide resin is treated with ethylmethyl-sulfide (EtSMe), ethanedithiol (EDT), and thioanisole (PhSMe) for approximately 20 min. prior to addition of 95% aqueous trifluoracetic acid (TFA). A total volume of approximately 50 ml of these reagents are used per gram of peptide-resin. The following ratio is used: TFA:EtSMe:EDT:PhSme (10:0.5:0.5:0.5). The mixture is stirred for 3 h at room temperature under an atmosphere of N_2. The mixture is filtered and the resin washed with TFA (2 x 3 ml). The combined filtrate is evaporated *in vacuo*, and anhydrous diethyl ether added to the yellow/orange residue. The resulting white precipitate is isolated by filtration. See King et al., 1990, Int. J. Peptide Protein Res. 36:255-266 regarding various cleavage methods.

6.10.3. <u>Purification of the Peptides</u>

Purification of the synthesized peptides can be carried out by standard methods including chromatography (*e.g.*, ion exchange, affinity, and sizing column chromatography, high performance liquid chromatography

(HPLC)), centrifugation, differential solubility, or by any other standard technique.

6.10.4. Conjugation of Peptides to Other Molecules

The peptides of the present invention may be linked to other molecules (*e.g.*, a detectable label, a molecule facilitating adsorption to a solid substratum, or a toxin, according to various embodiments of the invention) by methods that are well known in the art. Such methods include the use of homobifunctional and heterobifunctional cross-linking molecules.

The homobifunctional molecules have at least two reactive functional groups, which are the same. The reactive functional groups on a homobifunctional molecule include, for example, aldehyde groups and active ester groups. Homobifunctional molecules having aldehyde groups include, for example, glutaraldehyde and subaraldehyde. The use of glutaraldehyde as a cross-linking agent was disclosed by Poznansky et al., 1984, Science 223:1304-1306.

Homobifunctional molecules having at least two active ester units include esters of dicarboxylic acids and N-hydroxysuccinimide. Some examples of such N-succinimidyl esters include disuccinimidyl suberate and dithio-bis-(succinimidyl propionate), and their soluble bis-sulfonic acid and bis-sulfonate salts such as their sodium and potassium salts. These homobifunctional reagents are available from Pierce, Rockford, Illinois.

The heterobifunctional molecules have at least two different reactive groups. Some examples of heterobifunctional reagents containing reactive disulfide bonds include N-succinimidyl 3-(2-pyridyl-dithio)propionate (Carlsson et al., 1978, Biochem J. 173:723-737), sodium S-4-succinimidyloxycarbonyl-alpha-methylbenzylthiosulfate, and 4-succinimidyloxycarbonyl-alpha-methyl-(2-pyridyldithio)toluene. N-succinimidyl 3-(2-pyridyldithio)propionate is preferred. Some examples of

heterobifunctional reagents comprising reactive groups having a double bond that reacts with a thiol group include succinimidyl 4-(N-maleimidomethyl)cyclohexahe-1-carboxylate and succinimidyl m-maleimidobenzoate.

Other heterobifunctional molecules include succinimidyl 3-(maleimido)propionate, sulfosuccinimidyl 4-(p-maleimido-phenyl)butyrate, sulfosuccinimidyl 4-(N-maleimidomethyl-cyclohexane)-1-carboxylate, maleimidobenzoyl-N-hydroxy-succinimide ester. The sodium sulfonate salt of succinimidyl m-maleimidobenzoate is preferred. Many of the above-mentioned heterobifunctional reagents and their sulfonate salts are available from Pierce.

Additional information regarding how to make and use these as well as other polyfunctional reagents may be obtained from the following publications or others available in the art: Carlsson et al., 1978, Biochem. J. 173:723-737; Cumber et al., 1985, Methods in Enzymology 112:207-224; Jue et al., 1978, Biochem 17:5399-5405; Sun et al., 1974, Biochem. 13:2334-2340; Blattler et al., 1985, Biochem. 24:1517-152; Liu et al., 1979, Biochem. 18:690-697; Youle and Neville, 1980, Proc. Natl. Acad. Sci. USA 77:5483-5486; Lerner et al., 1981, Proc. Natl. Acad. Sci. USA 78:3403-3407; Jung and Moroi, 1983, Biochem. Biophys. Acta 761:162; Caulfield et al., 1984, Biochem. 81:7772-7776; Staros, 1982, Biochem. 21:3950-3955; Yoshitake et al., 1979, Eur. J. Biochem. 101:395-399; Yoshitake et al., 1982, J. Biochem. 92:1413-1424; Pilch and Czech, 1979, J. Biol. Chem. 254:3375-3381; Novick et al., 1987, J. Biol. Chem. 262:8483-8487; Lomant and Fairbanks, 1976, J. Mol. Biol. 104:243-261; Hamada and Tsuruo, 1987, Anal. Biochem. 160:483-488; Hashida et al., 1984, J. Applied Biochem. 6:56-63.

Additionally, methods of cross-linking are reviewed by Means and Feeney, 1990, Bioconjugate Chem. 1:2-12.

6.10.4.1. Biotinylation of Peptides

Methods of biotinylating peptides are well known in the art. Any convenient method may be employed in the

practice of the invention. For example, the following procedure was used. Ten micrograms of peptide was dissolved in 100 μl of 0.1 % acetic acid. PBS (900μl) and 3.3 mg of biotin-LC-NHS (Pierce, Rockford, IL) was added. Following incubation for 30 minutes at room temperature the biotinylated peptides were purified over a Superose 12 column (Pharmacia, Piscataway, NJ).

6.10.5. Synthetic Peptides

Tables 19, 20 and 21 provide the primary structure for various synthetic peptides manufactured in the practice of the present invention.

Table 19

Seq ID No	Peptide name	Sequence
	ELAN005	H_2N-C-K(dns)-FITKALGISYGRKKRRQRRRPPQGSQTHQVSLSKQ-$CONH_2$
	ELAN006	Ac-CLNGGVKMYVESVDRYVC-$CONH_2$
	FITC-ELAN006	Ac-CLNGGVK(FITC)MYVESVDRYVC-$CONH_2$
	ELAN006ii	H_2N-C-K(dns)-RLNGGVSMYVESVDRYVCR-$CONH_2$
167	ELAN007	H_2N-RIAGLPWYRCRTVAFETGMQNTQLCSTIVQLSFTPEE-COOH
193	ELAN007ii	H_2N-KKRIAGLPWYRCRTVAFETGMQNTQLCSTIVQLSFTPEE-$CONH_2$
	bZElan008 (P31)	biotin-K(dns)SARDSGPAEDGSRAVRLNGVENANTRKSSRSNPRGRRHP-COOH
	bZElan009	biotin-K(dns)SSADAEKCAGSLLWWGRQNNSGCGSPTKKHLKHRNRSQTSSSSHG-COOH
168	ELAN010	H_2N-REFAERRLWGCDDLSWRLDAEGCGPTPSNRAVKHRKPRPRSPAL-COOH
	bZElan010	biotin-K(dns)REFAERRLWGCDDLSWRLDAEGCGPTPSNRAVKHRKPRPRSPAL-COOH
169	ELAN012	H_2N-SGSHSGGMNRAYGDVFRELRDRWYATSHHTRPTPQLPRGPN-COOH
	bELAN012	biotin-SGSHSGGMNRAYGDVFRELRDRWYATSHHTRPTPQLPRGPN-COOH
	ZElan012	H_2N-K(dns)SGSHSGGMNRAYGDVFRELRDRWYATSHHTRPTPQLPRGPN-COOH

249	ELAN013	H_2N-SGSPPCGGSWGRFMQGGLFGGRTDGCGAHRNRTSASLEPPSSDY-$CONH_2$
250	ELAN014	H_2N-SHSGGMNRAYGDVFRELRDRWNATSHHTRPTPQLPRGPNS-$CONH_2$
	bZElan014	biotin-K(dns)SHSGGMNRAYGDVFRELRDRWNATSHHTRPTPQLPRGPNS-$CONH_2$
	ZElan014	H_2N-K(dns)SHSGGMNRAYGDVFRELRDRWNATSHHTRPTPQLPRGPNS-$CONH_2$
	ZElan015 (DCX11)	H_2N-K(dns)SQGSKQCMQYRTGRLTVGSEYGCGMNPARHATPAYPARLLPRYR-$CONH_2$
	ZElan016 (SNi10)	H_2N-K(dns)RVGQCTDSDVRRPWARSCAHQGCGAGTRNSHGCITRPLRQASAH-$CONH_2$
	bZElan017	biotin-K(dns)SGSGRVGQCTDSDVRRPWARSCA-$CONH_2$
	ZElan017	H_2N-K(dns)RVGQCTDSDVRRPWARSCA-$CONH_2$
	ZElan018 (PAX2)	H_2N-K(dns)STPPSREAYSRPYSVDSDSDTNAKHSSHNRRLRTRSRPNG-$CONH_2$
	ZElan019 (5PAX5)	H_2N-K(dns)RGSTGTAGGERSGVLNLHTRDNASGSGFKPWYPSNRGHK-$CONH_2$
	ZElan020 (CY09)	H_2N-K(dns)SGSGLYANPGMYSRLHSPA-$CONH_2$
	bZElan020 (CY09)	biotin-K(dns)SGSGLYANPGMYSRLHSPA-$CONH_2$
	ZElan021 (HAX42)	H_2N-K(dns)SDHALGTNLRSDNAKEPGDYNCCGNGNSTGRKVFNRRRPSAIPT-$CONH_2$
	ZElan022 (SNi34)	H_2N-K(dns)SPCGGSWGRFMQGGLFGGRTDGCGAHRNRTSASLEPPSSDY-$CONH_2$
	ZElan023 (DCX8)	H_2N-K(dns)RYKHDIGCDAGVDKKSSSVRGGCGAHSSPPRAGRGPRGTMVSRL-$CONH_2$
	ZElan024 (P31)	H_2N-K(dns)SARDSGPAEDGSRAVRLNGVENANTRKSSRSNPRGRRHPGG-$CONH_2$
	ZElan025 (DAB10)	H_2N-K(dns)SKSGEGGDSSRGETGWARVRSHAMTAGRFRWYNQLPSDR-$CONH_2$
	ZElan026 (PAX2/control)	H_2N-K(dns)SEANLDGRKSRYSSPRRNSSTRPRTSPNSVHARYPSTDHD-$CONH_2$
	bELAN027 (PAX2)	biotin-SGSGSTPPSREAYSRPYSVDSDSDTNAKHSSHNRRLRTRSRPNG-$CONH_2$
251	18C21	H_2N-DTNAKHSSHNRRLRTRSRPNG-$CONH_2$
	Fmoc-Z16N23	Fmoc-K(dns)RVGQCTDSDVRRPWARSCAHQG-COOH
252	16C23	H_2N-CGAGTRNSHGCITRPLRQASAHG-$CONH_2$

Z16C23	H_2N-K(dns)CGAGTRNSHGCITRPLRQASAHG-$CONH_2$
ZElan028 (P31 fragment)	H_2N-K(dns)ENANTRKSSRSNPRGRRHPG-$CONH_2$
ZElan029 (P31 fragment)	H_2N-K(dns)TRKSSRSNPRG-$CONH_2$
ZElan030 (P31 fragment)	H_2N-K(dns)ENANTRKSSRSNPRG-$CONH_2$
ZElan031 (P31 fragment)	H_2N-K(dns)TRKSSRSNPRGRRHPG-$CONH_2$
ZElan032 (PAX2 fragment)	H_2N-K(dns)TNAKHSSHNRRLRTRSRPN-$CONH_2$
ZElan033 (PAX2 fragment)	H_2N-K(dns)TNAKHSSHNRRLRTR-$CONH_2$
ZElan034 (PAX2 fragment)	H_2N-K(dns)SSHNRRLRTRSRPN-$CONH_2$
ZElan035 (PAX2 fragment)	H_2N-K(dns)SSHNRRLRTR-$CONH_2$
ZElan036 (SNi10 fragment)	H_2N-K(dns)VRRPWARSCAHQGCGAGTRNS-$CONH_2$
ZElan037 (SNi10 fragment)	H_2N-K(dns)CTDSDVRRPWARSC-$CONH_2$
ZElan038 (PAX2/control)	H_2N-K(dns)SRANTDGRKSRYSSPRRNSSTEPRLSPNSVHARYPSTDHD-$CONH_2$
ZElan039 (P31 fragment)	H_2N-K(dns)ENANTRKSSR-$CONH_2$
ZElan040 (P31 fragment)	H_2N-K(dns)SNPRGRRHPG-$CONH_2$
ZElan041 (P31 fragment)	H_2N-K(dns)ENANT-$CONH_2$
ZElan042 (P31 fragment)	H_2N-K(dns)ANTRKS-$CONH_2$
ZElan043 (P31 fragment)	H_2N-K(dns)TRKSS-$CONH_2$
ZElan044 (P31 fragment)	H_2N-K(dns)RKSSR-$CONH_2$
ZElan045 (P31 fragment)	H_2N-K(dns)KSSRSN-$CONH_2$

ZElan046 (P31 fragment)	H_2N-K(dns)SSRSNPG-$CONH_2$
ZElan047 (P31 fragment)	H_2N-K(dns)RSNPRG-$CONH_2$
ZElan048 (P31 fragment)	H_2N-K(dns)SNPRG-$CONH_2$
ZElan049 (P31 fragment)	H_2N-K(dns)PRGRRH-$CONH_2$
ZElan050 (P31 fragment)	H_2N-K(dns)RRHPG-$CONH_2$
ZElan051 (HepC)	H_2N-K(dns)KSSRGN-$CONH_2$
ZElan052 (HepC)	H_2N-K(dns)KTSERSQPRGRRQPG-$CONH_2$
ZElan053 (P31 analog)	H_2N-K(dns)TrKSSrSNPrGrrHPG-$CONH_2$
ZElan054 (P31 analog)	H_2N-K(dns)TRKSSrSNPRGrRHPG-$CONH_2$
ZElan055 (PAX2 fragment)	H_2N-K(dns)TNAKHSSHN-$CONH_2$
ZElan056 (PAX2 fragment)	H_2N-K(dns)RRLRTRSRPN-$CONH_2$
ZElan057 (PAX2 fragment)	H_2N-K(dns)RRLRTRSR-$CONH_2$
ZElan058 (PAX2 fragment)	H_2N-K(dns)RRLRTR-$CONH_2$
ZElan059 (PAX2 analog)	H_2N-K(dns)rrLrTrSrPN-$CONH_2$
ZElan060 (HAX42 fragment)	H_2N-K(dns)SDHALGTNLRSDNAKEPGDYNCCGNG-$CONH_2$
ZElan061 (HAX42 fragment)	H_2N-K(dns)GDYNCCGNGNSTGRKVFNRRRPSAIPT-$CONH_2$
ZElan062 (HAX42 fragment)	H_2N-K(dns)SDHALGTNLRSDNAKEPG-$CONH_2$
ZElan063 (HAX42 fragment)	H_2N-K(dns)GDYNCCGNGNSTG-$CONH_2$
ZElan064 (HAX42 fragment)	H_2N-K(dns)RKVFNRRRPSAIPT-$CONH_2$

	ZElan065 (HAX42 fragment)	H_2N-K(dns)RKVFNRRRPS-$CONH_2$
	ZElan066 (HAX42 fragment)	H_2N-K(dns)NRRRPSAIPT-$CONH_2$
	ZElan067 (HAX42 fragment)	H_2N-K(dns)NRRRPS-$CONH_2$
55	Elan018 (PAX2 no dns)	H_2N-STPPSREAYSRPYSVDSDSDTNAKHSSHNRRLRTRSRPNG-$CONH_2$
52	Elan021 (HAX42 no dns)	H_2N-SDHALGTNLRSDNAKEPGDYNCCGNGNSTGRKVFNRRRPSAIPT-$CONH_2$
	ZElan070 (HAX42 fragment)	H_2N-K(dns)SDHALGTNLRSDNAKEPGDYNCCGNGNST-$CONH_2$
	ZElan071 (HAX42 fragment)	H_2N-K(dns)NLRSDNAKEPGDYNCCGNGNSTGRKVFNR-$CONH_2$
	ZElan072 (HAX42 fragment)	H_2N-K(dns)PGDYNCCGNGNSTGRKVFNRRPSAIPT-$CONH_2$
	ZElan073 (PAX2 fragment)	H_2N-K(dns)ASHNRRLRTR-$CONH_2$
	ZElan074 (PAX2 fragment)	H_2N-K(dns)SAHNRRLRTR-$CONH_2$
	ZElan075 (PAX2 fragment)	H_2N-K(dns)SSANRRLRTR-$CONH_2$
	ZElan076 (PAX2 fragment)	H_2N-K(dns)SSHARRLRTR-$CONH_2$
	ZElan077 (PAX2 fragment)	H_2N-K(dns)SSHNARLRTR-$CONH_2$
	ZElan078 (PAX2 fragment)	H_2N-K(dns)SSHNRALRTR-$CONH_2$
	ZElan079 (PAX2 fragment)	H_2N-K(dns)SSHNRRARTR-$CONH_2$
	ZElan080 (PAX2 fragment)	H_2N-K(dns)SSHNRRLATR-$CONH_2$
	ZElan081 (PAX2 fragment)	H_2N-K(dns)SSHNRRLRAR-$CONH_2$
	ZElan082 (PAX2 fragment)	H_2N-K(dns)SSHNRRLRTA-$CONH_2$
	Elan035	H_2N-SSHNRRLRTR-$CONH_2$

	ZElan083 (PAX2/control)	H_2N-K(dns)GRNHDVVSSNTHKSYRSPRSASYPRLSNDRTDRTEPAPSS-$CONH_2$
	ZElan084 (PAX2/control)	H_2N-K(dns)RNTRNKTSRLSANPHRSHR-$CONH_2$
	Elan032Z (PAX2 fragment)	H_2N-TNAKHSSHNRRLRTRSRPN K(dns)-$CONH_2$
	Elan057Z (PAX2 fragment)	H_2N-RRLRTRSRK(dns)-$CONH_2$

TABLE 20

Name	Description	Sequence
ZElan087	HAX42-1 (20 mer)	H_2N-K(dns)SDHALGTNLRSDNAKEPGDY
ZElan088	HAX42-2 (20 mer)	H_2N-K(dns)SDNAKEPGDYNCCGNGNSTG
ZElan089	HAX42-3 (15 mer)	H_2N-K(dns)SDHALGTNLRSDNAK
ZElan090	HAX42-4 (15 mer)	H_2N-K(dns)EPGDYNCCGNGNSTG
ZElan091	HAX42-5 (14 mer)	H_2N-K(dns)PGDYNCCGNGNSTG
ZElan092	HAX42-6 (10 mer)	H_2N-K(dns)PGDYNCCGNG
ZElan093	HAX42-7 (10 mer)	H_2N-K(dns)NCCGNGNSTG
ZElan100	P31 16 mer cyclic	H_2N-K(dns)Lys-TRKSSRSNPRGRRHPG
ZElan101	P31 16 mer cyclic D form	H_2N-K(dns)Lys-TrKSSrSNPrGrrHPG
ZElan103	PAX2 15 mer cyclic	H_2N-K(dns)Lys-TNAKHSSHNRRLRTR
ZElan103A	PAX2 15 mer cyclic (internal)	H_2N-K(dns)TNAKHSSCNRRCRTR
ZElan104	PAX2 15 mer cyclic (internal)	H_2N-K(dns)TNAKHSSCNRRLRCR
ZElan105	PAX2 Ala Scan 1	H_2N-K(dns)ANAKHSSHNRRLRTR
ZElan106	PAX2 Ala Scan 2	H_2N-K(dns)TAAKNSSHNRRLRTR
ZElan107	PAX2 Ala Scan 3	H_2N-K(dns)TNGKNSSHNRRLRTR
ZElan108	PAX2 Ala Scan 4	H_2N-K(dns)TNAAHSSHNRRLRTR
ZElan109	PAX2 Ala Scan 5	H_2N-K(dns)TNAKASSHNRRLRTR
ZElan110	PAX2 Ala Scan 6	H_2N-K(dns)TNAKHASHNRRLRTR
ZElan111	PAX2 Ala Scan 7	H_2N-K(dns)TNAKHSAHNRRLRTR
ZElan112	PAX2 Ala Scan 8	H_2N-K(dns)TNAKHSSANRRLRTR

ZElan113	PAX2 Ala Scan 9	H_2N-K(dns)TNAKHSSHARRLRTR
ZElan114	PAX2 Ala Scan 10	H_2N-K(dns)TNAKHSSHNARLRTR
ZElan115	PAX2 Ala Scan 11	H_2N-K(dns)TNAKHSSHNRALRTR
ZElan116	PAX2 Ala Scan 12	H_2N-K(dns)TNAKHSSHNRRARTR
ZElan117	PAX2 Ala Scan 13	H_2N-K(dns)TNAKHSSHNRRLATR
ZElan118	PAX2 Ala Scan 14	H_2N-K(dns)TNAKHSSHNRRLRAR
ZElan119	PAX2 Ala Scan 15	H_2N-K(dns)TNAKHSSHNRRLRTA
ZElan123	PAX2 15 mer cyclic D form	H_2N-K(dns)Lys-TNAKHSSHNrrLrTr
ZElan124	PAX2 15 mer D form	H_2N-K(dns)TNAKHSSHNrrLrTr
ZElan125	PAX2 10 mer cyclic	H_2N-K(dns)Lys-SSHNRRLRTR
ZElan126	PAX2 10 mer cyclic D form	H_2N-K(dns)Lys-SSHNrrLrTr
ZElan127	PAX2 10 mer cyclic	H_2N-K(dns)Lys-TNAKHSSHNR
ZElan128	PAX2 10 mer cyclic D form	H_2N-K(dns)Lys-TNAKHSSHNr
ZElan129	PAX2 15 mer	H_2N-K(dns)TNAKHSSHNRRLRTR
ZElan130	HAX42 14 mer Ala Scan 1	H_2N-K(dns)AGDYNCCGNGNSTG
ZElan131	HAX42 14 mer Ala Scan 2	H_2N-K(dns)PADYNCCGNGNSTG
ZElan132	HAX42 14 mer Ala Scan 3	H_2N-K(dns)PGAYNCCGNGNSTG
ZElan133	HAX42 14 mer Ala Scan 4	H_2N-K(dns)PGDANCCGNGNSTG
ZElan134	HAX42 14 mer Ala Scan 5	H_2N-K(dns)PGDYACCGNGNSTG
ZElan135	HAX42 14 mer Ala Scan 6	H_2N-K(dns)PGDYNACGNGNSTG
ZElan136	HAX42 14 mer Ala Scan 7	H_2N-K(dns)PGDYNCAGNGNSTG
ZElan137	HAX42 14 mer Ala Scan 8	H_2N-K(dns)PGDYNCCANGNSTG
ZElan138	HAX42 14 mer Ala Scan 9	H_2N-K(dns)PGDYNCCGAGNSTG
ZElan139	HAX42 14 mer Ala Scan 10	H_2N-K(dns)PGDYNCCGNANSTG
ZElan140	HAX42 14 mer Ala Scan 11	H_2N-K(dns)PGDYNCCGNGASTG
ZElan141	HAX42 14 mer Ala Scan 12	H_2N-K(dns)PGDYNCCGNGNATG
ZElan142	HAX42 14 mer Ala Scan 13	H_2N-K(dns)PGDYNCCGNGNSAG
ZElan143	HAX42 14 mer Ala Scan 14	H_2N-K(dns)PGDYNCCGNGNSTA

GST fusion proteins of GIT peptides are shown in Table 21.

Table 21

Source	Clone #	GST Fusion Sequence	SEQ ID NO.
DCX11	98	gst-SQGSKQCMQYRTGRLTVGSEYGCGMNPARHATPAYPARLLPRYR	213
HAX42	99	gst-SDHALGTNLRSDNAKEPGDYNCCGNGNSTGRKVFNRRRPSAIPT	214
SNi34	100	gst-SPCGGGSWGRFMQGGLFGGRTDGCGAHRNRTSASLEPPSSDY	215
5PAX5	97	gst-RGSTGTAGGERSGVLNLHTRDNASGSGFKPWYPSNRGHK	216
SNi28	84	gst-SHSGGMNRAYGDVFRELRDRWNATSHHTRPTPQLPRGPN	217
SNi28	85	gst-SHSGGMNRAY	218
SNi28	86	gst-GDVFRELRDR	219
SNi28	87	gst-WNATSHHTRP	220
SNi28	88	gst-TPQLPRGPN	221
SNi28	89	gst-GDVFRELRDRWNATSHHTRP	222
SNi28	90	gst-WNATSHHTRPTPQLPRGPN	223
SNi28	91	gst-GDVFRELRDRWNATSHHTRPTPQLPRGPN	224
SNi28	92	gst-SHSGGMNRAYGDVFRELRDRWNATSAATRPTPQLPRGPN	225
P31	93	gst-SARDSGPAEDGSRAVRLNGVENANTRKSSRSNPRGRRHP	226
P31	101	gst-SARDSGPAEDGSRAVRLNG	227
P31	102	gst-DGSRAVRLNGVENANTRKSSR	228
P31	103	gst-ENANTRKSSRSNPRGRRHP	229
P31	110	gst-ENANTRKSSR	230

P31	111	gst-RKSSRSNPRG	
P31	112	gst-SNPRGRRHP	232
P31	119	gst-TRKSSRSNPRG	233
PAX2	94	gst-STPPSREAYSRPYSVDSDSDTNAKHSSHNRRLRTRSRPN	234
PAX2	104	gst-STPPSREAYSRPYSVDSDSD	235
PAX2	105	gst-SRPYSVDSDSDTNAKHSSHNR	236
PAX2	106	gst-TNAKHSSHNRRLRTRSRPN	237
PAX2	113	gst-TNAKHSSHN	238
PAX2	114	gst-SSHNRRLRTR	239
PAX2	115	gst-RRLRTRSRPN	240
SNi10	96	gst-RVGQCTDSDVRRPWARSCAHQGCGAGTRNSHGCITRPLRQASAH	241
SNi10	116	gst-RVGQCTDSDVRRPWARSCA	242
SNi10	117	gst-VRRPWARSCAHQGCGAGTRNS	243
SNi10	118	gst-GTRNSHGCITRPLRQASAH	244
DCX8	95	gst-RYKHDIGCDAGVDKKSSSVRGGCGAHSSPPRAGRGPRGTMVSRL	245
DCX8	107	gst-RYKHDIGCDAGVDKKSSSVRGGCG	246
DCX8	108	gst-GCDAGVDKKSSSVRGGCGAHSSPPRA	247
DCX8	109	gst-GAHSSPPRAGRGPRGTMVSRL	248

6.10.6. Peptide Stability

The relative stability for ZElan031, ZElan053 and ZElan054 was determined in simulated intestinal fluid (SIF) SIF was made by dissolving 100mg of pancreatin (Sigma cat#P-1625, lot# 122H0812)in 8.4ml of phosphate stock solution, adjusting the pH to 7.5 with 0.2N NaOH and adjusting the volume to 10ml with water.

Peptide (3.25mg) was dissolved in 3.25 ml of 10,000 fold diluted SIF solution at 37°C. Aliquots (0.7ml) of the digestion solution were then withdrawn at <1min, 1h, 3h, and 21h or 24h. The samples were quickly passed through a syringe filter (Millipore Millex-GV 0.22μm, part# SLGV025LS, lot# H2BM95250) and 300μL of the filtered solution was immediately injected onto a Hewlett-Packard HPLC system equipped with a C-8 column (Applied Biosystems column and guard column: column- p/n 0711-0023 Spheri-5 ODS 5μm, 220x4.6mm). The products were eluted at 1.5ml/min using an acetonitrile-water gradient. The major fluorescent peaks were collected, lyopholized and identified by MS analysis.

The HPLC gradient used was:

Time (min)	Solvent Mixture	
0	95% H_2O-5% acetonitrile (0.1%TFA)	
5	95% H_2O-5%acetonitrile (0.1%TFA)	
35	85% H_2O-15% acetonitrile (0.1%TFA)	linear solvent change
40	0% H_2O-100% acetonitrile (0.1%TFA)	"
45	95% H_2O-5% acetonitrile (0.1%TFA)	"
52	95% H_2O-5%acetonitrile (0.1%TFA)	"

As shown in Table 22, the relative stability (to SIF) for the three peptides was found to be ZElan053>ZElan054>ZElan031. Enzymatic cleavage of the peptide was found to occur at arginine and/or lysine as expected. The replacement of l-amino acids with their D-amino acid analogs significantly reduced the rate of proteolysis at these residues.

TABLE 22

Peptide	Percent Remaining at:				Rel. Stab.
	1 m	1 h	3 h	24 h	
ZElan031	100	38.7	0	0	3
ZElan054	97.4	58.2	11.6	2.7	2
ZElan053	100	98.3	98.1	94.0	1

7. CHARACTERIZATION OF PEPTIDE-COATED PARTICLES

Binding of Peptide-Coated PLGA Nanoparticles to Fixed Caco-2 Cells

Binding of nanoparticles coated with targeting peptides to fixed Caco-2 cells was investigated using an ELISA assay based on reaction of antibody with the dansyl moiety present on the peptides. Isoelectric points of selected synthetic peptides are shown in Table 23 (corresponding SEQ ID NOS. are shown in Table 7). Corresponding dansylated synthetic GIT binding peptides are given in Table 24.

TABLE 23

Peptide	Sequence	pI
P31	SARDSGPAEDGSRAVRLNGVENANTRKSSRSNPRGRRHP	12.26
5PAX5	RGSTGTAGGERSGVLNLHTRDNASGSGFKPWYPSNRGHK	11.49
SNi10	RVGQCTDSDVRRPWARSCAHQGCGAGTRNSHGCITRPLRQASAH	10.45
SNi34	SPCGGSWGRFMQGGLFGGRTDGCGAHRNRTSASLEPPSSDY	8.25
DCX11	SQGSKQCMQYRTGRLTVGSEYGCGMNPARHATPAYPARLLPRYR	10.44
DCX8	RYKHDIGCDAGVDKKSSSVRGGCGAHSSPPRAGRGPRGTMVSRL	11.03
HAX42	SDHALGTNLRSDNAKEPGDYNCCGNGNSTGRKVFNRRRPSAIPT	9.62
PAX2	STPPSREAYSRPYSVDSDSDTNAKHSSHNRRLRTRSRPN	11.26

TABLE 24

Peptide	Sequence
P31	H_2N-K(dns)SARDSGPAEDGSRAVRLNGVENANTRKSSRSNPRGRRHPGG-$CONH_2$
5PAX5	H_2N-K(dns)RGSTGTAGGERSGVLNLHTRDNASGSGFKPWYPSNRGHK-$CONH_2$
SNi10	H_2N-K(dns)RVGQCTDSDVRRPWARSCAHQGCGAGTRNSHGCITRPLRQASAH-$CONH_2$
SNi34	H_2N-K(dns)SPCGGSWGRFMQGGLFGGRTDGCGAHRNRTSASLEPPSSDY-$CONH_2$
DCX11	H_2N-K(dns)SQGSKQCMQYRTGRLTVGSEYGCGMNPARHATPAYPARLLPRYR-$CONH_2$
DCX8	H_2N-K(dns)RYKHDIGCDAGVDKKSSSVRGGCGAHSSPPRAGRGPRGTMVSRL-$CONH_2$
HAX42	H_2N-K(dns)SDHALGTNLRSDNAKEPGDYNCCGNGNSTGRKVFNRRRPSAIPT-$CONH_2$
PAX2	H_2N-K(dns)STPPSREAYSRPYSVDSDSDTNAKHSSHNRRLRTRSRPNG-$CONH_2$
DAB10	H_2N-K(dns)SKSGEGGDSSRGETGWARVRSHAMTAGRFRWYNQLPSDR-$CONH_2$

Method:

Confluent Caco-2 monolayers grown in 96-well plates (p38) were fixed and treated with 0.1% phenylhydrazine before blocking with 0.1% BSA in PBS. Control and dansyl peptide-coated nanoparticles were resuspended in sterile water at 10mg/ml and stirred with a magnet for 1h at room temperature. Samples consisted of: (1) blank nanoparticle control, (2) scrambled PAX2-coated nanoparticles, (3) PAX2-coated nanoparticles, (4) HAX42-coated nanoparticles, (5) PAX2/HAX42-coated nanoparticles, and (6) 8 peptide-coated nanoparticles.

Nanoparticles were added to the cells at 10mg/ml in 100μl 1%BSA-PBS (no Tween80 is used in this assay) and 2-fold serially-diluted. The 96-well plates were incubated for 1h at room temperature. The plates were washed 5 times with 1%BSA-PBS and 100μl of anti-dansyl antibody (Cytogen DB3-226.3; 0.5 μg/ml; batch May 1997) was added per well and the plates incubated 1h at room temperature. The wells were washed 5 times with 1%BSA-PBS; 100μl of goat anti-mouse λ:HRP antibody (Southern Biotechnology CN. 1060-05; 1:10,000) was added per well, and the plates incubated 1h at room temperature. After washing 5 times with 1%BSA-PBS, 100μl of TMB peroxidase substrate (KPL CN. 50-76-00) was added to the wells and the optical density at 650nm was measured after 15 minutes.

As shown in Figures 13A-B, a decreasing anti-dansyl ELISA response was observed for nanoparticles coated with PAX2, HAX2, PAX2+HAX2, and a mixture of 8 targeting peptides, when decreasing amounts of the nanoparticles were applied to fixed Caco-2 cells. No concentration effect was observed for blank nanoparticles or nanoparticles coated with a scrambled version of PAX2 peptide. Nanoparticles coated with PAX2, HAX2, PAX2+HAX2, and the 8 peptide mix, showed increased response relative to blank nanoparticles or nanoparticles coated with a scrambled version of PAX2 peptide. The OD values were low relative to those normally observed for GST-peptide fusion binding to fixed Caco-2 cells.

Table 25 below shows the insulin potency and level of peptides coated onto the particles (measured by fluorescense) for formulation 1 particles (formulation by the coacervation method given below).

Table 25

Peptide	**Blend**	
	Insulin mg/g	*Peptide* µl/mg
PAX2	60.7	3.51
HAX42	55.9	2.93
PAX2 SCRAMBLED	57.7	1.26
P31	67.0	1.22
5PAX5	52.7	2.83
SNi10	59.5	1.75
SNi34	61.5	4.03
DCX8	59.1	1.87
DAB10	55.9	1.99

ELISA of dansylated peptides and insulin coated PLGA particles

The standard ELISA procedure was modified as follows. Peptides and particles were diluted to an appropriate concentration in PBS containing 1%BSA (particles were sonicated to achieve a homogeneous solution), titered

and incubated one hour at room temperature. Following five washes with PBS containing 1%BSA, an in-house IgG1λ anti-dansyl monoclonal antibody was added (diluted to 1μg/ml in 1%BSA-PBS) and the plates were incubated for one hour. After five more washes goat anti-mouse λ-HRP was added (Southern Biotechnology Associates Inc., Birmingham, AL, diluted 1:10,000 in 1%BSA-PBS) and the plates were incubated one hour. After five washes, plates were developed with TMB peroxidase substrate (Kirkegard and Perry, Gaithersburg, MD). All data is presented with background binding subtracted. Tween 20 was not added to the diluent or the washes when insulin coated PLGA particles were included in the assay.

Figures 14A-14B show the binding of the dansylated peptide SNi10 to hSI and BSA.

8. BINDING OF SYNTHETIC PEPTIDES AND PEPTIDE-COATED PARTICLES TO S100 AND P100 FRACTIONS DERIVED FROM CACO-2 CELLS

8.1. Detection of Binding to Membrane (P100) and Cytosolic (S100) fractions

Caco-2 cell membrane (P100) and cytosolic (S100) fractions were prepared using a modification of the method described in Kinsella, B. T., O'Mahony, D. J. and G. A. FitzGerald, 1994, J. Biol. Chem. 269(47): 29914-29919. Confluent Caco-2 cell monolayers (grown in 75 cm^2 flasks for up to 1 week at 37°C and 5% CO_2) were washed twice in Dulbecco's PBS (DPBS) and the cells were harvested by centrifugation at 1000 rpm after treatment with 10 mM EDTA-DPBS. The cells were washed 3 times in DPBS and the final cell pellet was resuspended in 3 volumes of ice cold HED buffer (20 mM HEPES (pH 7.67), 1 mM EGTA, 0.5 mM dithiothreitol, 1 mM phenylmethylsulphonyl fluoride (PMSF)). The cells were allowed to swell for 5 min on ice prior to homogenization for 30 sec. The homogenates were centrifuged at 40,000 rpm for 45 min at 4°C. The supernatant (S100) was

removed and the pellet (P100) was resuspended in HEDG buffer (20 mM HEPES (pH 7.67), 1 mM EGTA, 0.5 mM dithiothreitol, 100 mM NaCl, 10% glycerol, 1 mM PMSF). Protein concentrations were determined using the Bradford assay (Bradford, M. M., 1976, Anal. Biochem. 72: 248-254).

Binding of peptide and/or peptide-coated PLGA particles to membrane (P100) and cytosolic (S100) fractions was assessed by detection of the dansyl moiety incorporated in the peptide. Costar ninety six well ELISA plates were coated with S100 and P100 fractions (100 μg/ml in 0.05 M $NaHCO_3$) overnight at 4°C. The plates were blocked with 0.5% bovine serum albumin in DPBS for 1 h at room temperature and washed 3 times in 1% BSA-DPBS. Peptide-coated particles or peptides were dispersed in the same buffer and added to the plates at concentrations in the range 0.0325 - 0.5 mg/well. After 1 h at room temperature the plates were washed 5 times in 1% BSA-DPBS and 100 μl of anti-dansyl antibody (Cytogen DB3-226.3; 0.5 μg/ml) was added per well. The plates were incubated for 1 h at room temperature. The wells were washed 3 times in 1% BSA-DPBS and 100 μl of goat anti-mouse IgGλ:HRP antibody (Southern Biotechnology 1060-05; 1:10,000) was added per well. The plates were incubated for 1 h at room temperature. After washing 3 times in 1% BSA-DPBS 100 μl of TMB substrate (3,3',5',5-tetramethylbenzidine; Microwell Peroxidase Substrate System (Kirkegaard and Perry Laboratories 50-76-00)) was added and the optical density was measured at 650 nm at various time intervals.

8.2. Binding of Peptide-Coated PLGA particles

A novel assay system is provided by the instant invention for detection of binding of peptide-coated PLGA particles to membrane (P100) and cytosolic (S100) fractions derived from live Caco-2 cells. The absorbance readings obtained using this assay system were substantially higher than those obtained using similar peptide-coated PLGA particle concentrations on fixed Caco-2 cells. This greater sensitivity together with the derivation of the S100 and P100

fractions from live Caco-2 cells suggests that this assay may be the assay system of choice for detection of peptide-coated PLGA particle binding. The assay was concentration dependent and peptide/particle correlation permitted differentiation between specific and non-specific binding interactions.

Binding of peptide-coated PLGA particles was assessed using S100 and P100 fractions derived from live Caco-2 cells as described above. The fractions were coated onto 96-well plates at 10μg/well in 0.05 M $NaHCO_3$ and peptide-coated PLGA particles were assayed by ELISA at concentrations in the range 0.0325 - 0.5 mg/well.

Figures 15A and 15B illustrate the data obtained on S100 and P100 fractions respectively for particles coated with no peptide, scrambled PAX2 (control), P31 D-Arg 16-mer (ZElan053), HAX42, PAX2 and HAX42/PAX2. Using particle concentrations of 0.0325 - 0.5 mg/well all test peptide-coated PLGA particles exhibited greater binding to both the S100 and P100 fractions than the scrambled PAX2 coated control particles. All particles except P31 D-Arg 16-mer (ZElan053) exhibited greater binding to the P100 fraction than the S100 fraction. Greater binding of the P31 D-Arg 16-mer (ZElan053) coated particles to the S100 fraction may be indicative of non-specific binding due to the D-Arg modification of the P31 peptide (SEQ ID NO:43).

Binding of PLGA particles coated with varying concentrations of PAX2 peptide ranging from 0.05 - 5.0 mg/g was assessed using a) fixed Caco-2 cells (P35) and b) S100 and P100 fractions (Caco-2 P33). The particles were assayed at concentrations in the range 0.03125 - 0.0625 mg/well.

Using a particle concentration of 0.0625 mg/well, all PAX2 coated particles except those coated at 0.05 mg/g exhibited greater binding to fixed Caco-2 cells than the scrambled PAX2 coated control particles. There appeared to be a concentration effect with increasing PAX2 peptide concentration resulting in improved Caco-2 cell binding (in the range 0.05 - 1.0 mg/g). However all absorbance readings

were low and binding of the PAX2 (5 mg/g) was not consistent with this pattern.

Using particle concentrations of 0.03125 - 0.0625 mg/well all test peptide coated particles except PAX2 (0.05 mg/g) exhibited comparable or greater binding to both the S100 and P100 fractions than the scrambled PAX2 coated control particles. All particles exhibited greater binding to the P100 fraction than the S100 fraction. Binding to both the S100 and P100 fractions was directly proportional to the concentration of the PAX2 peptide on the particle. The absorbance readings obtained using this assay system were substantially higher than those obtained on the fixed Caco-2 cells.

The effect of blocking solution on binding of peptide-coated PLGA particles to P100 fractions (Caco-2 P35) was assessed using 1% bovine serum albumin (BSA) and 1% milk powder blocking solutions to assess background binding. The following particles were assayed at concentrations in the range 0.03125 - 0.0625 mg/well: no peptide; scrambled PAX2; and a range of PAX2 coated particles having peptide concentrations from 5-0.05 mg/g. As previously observed using 1% BSA, all test peptide coated particles except PAX2 coated at 0.05 mg/g exhibited comparable or greater binding to the P100 fractions than the scrambled PAX2 coated control particles. Binding to P100 fractions was directly proportional to the concentration of the PAX2 peptide on the particle (although in this instance PAX2 (5 mg/g) exhibited slightly lower binding than PAX2 (1 mg/g)). A similar trend was observed using 1% milk powder and a particle concentration of 0.0625 mg/well. However all absorbance readings were low when 1% milk powder was used and the binding pattern was not detectable using particles at a concentration of 0.0625 mg/well.

Non-specific binding of peptide-coated PLGA particles to plastic was also assessed using 1% BSA and 1% milk powder blocking solutions. The binding pattern observed above could be detected when BSA was used; however, absorbance readings

were substantially lower and binding of particles PAX2 (0.1 and 0.05 mg/g respectively) was not detectable. When 1% milk powder was used, all absorbance readings were low and no binding pattern was detectable. BSA was chosen for blocking in subsequent assays.

8.3. Comparison of Peptide-Coated Particle and Synthetic Peptide Binding to P100 fractions

Binding of dansylated peptides to P100 fractions was assessed to determine if peptide binding was predictive of peptide-coated particle binding. Figure 16 illustrates the data obtained for the dansylated peptides A) HAX42, P31 D-form and scrambled PAX2 and B) PAX2, HAX42 and scrambled PAX2.

Two consecutive assays produced substantial variations in absorbance readings. Initially, the HAX42 peptide exhibited strong binding when compared to the scrambled PAX2 control. The P31 D-form peptide (ZElan053) exhibited binding at the highest dilution only. In the repeat assay, HAX42 also exhibited significant binding compared to the scrambled PAX2 control. However, the scrambled PAX2 control and HAX42 produced relatively high absorbance values compared to those obtained in the previous assay. The PAX2 peptide was indistinguishable from the scrambled PAX2 control. Peptide/particle binding correlation is summarized as follows in Table 26:

TABLE 26

Peptide/particle assay correlation

Peptide	Assay correlation
HAX42	+
PAX2	+/-
P31 D-form	-
Scrambled PAX2	+/-

+ positive; +/- equivocal; - negative

Peptide/particle binding correlated well for the HAX42 peptide. In contrast, no correlation could be detected

for the P31 D-form (ZElan053) peptide. Since the P31 D-form peptide-coated particles exhibited greater binding to the S100 fraction than the P100 fraction (unlike the other test peptides) it appears that the particle binding interaction was non-specific or that some other molecule was competing for binding to the P100 fraction but not to the S100 fraction. Thus the peptide/particle assay correlation may be useful for distinguishing between specific and non-specific binding interactions. The scrambled PAX2 control produced variable results so that it was difficult to assess the PAX2 binding correlation.

8.4. Determination of HAX42 and PAX2 Binding Motif Sequences

Peptides and GST fusion proteins of HAX42, PAX2 and various derivatives were assayed using peptide ELISA to P100 membrane fractions derived from Caco-2 cells. The GST-PAX2 protein and PAX2 peptide data indicate that a core binding motif lies in the amino acid sequence TNAKHSSHNRRLRTR (SEQ ID NO:) otherwise named GST-106 and ZElan033. Similarly, the HAX42 peptide data suggest that a core binding motif for HAX42 lies in the amino acid sequence PGDYNCCGNCNSTG (SEQ ID NO:), otherwise named ZElan091.

The peptides and proteins were analyzed by a dansylated peptide ELISA method in which 96 well plates were coated overnight at 4°C with 100μl/well coating protein (normally 100μg/ml P100 membrane fraction) in 0.05M carbonate buffer pH9.6. Nonspecific binding was blocked using 200μl/well, 2% Marvel/PBS for 2 hours at 37°C prior to incubation with dansylated peptides. The plates were washed three times with PBS/0.05% Tween 20 and after each subsequent incubation step. The peptides were diluted in blocking solution at a starting concentration of 100μg/ml and diluted 1:2 downwards, 100μl/well, followed by incubation at room temperature for 1 hour, exactly. A buffer blank control was included to ensure that background binding to plastic was not due to the antibodies used in the assay system. To detect the

dansylated peptides, a mouse anti-dansyl antibody (DB3, Cytogen Corp.) at 1:1340 dilution in blocking buffer and 100μl/well was added followed by incubation at room temperature for 1 hour. The plates were then incubated with an anti-mouse λ-HRP conjugated antibody (Southern Biotech 1060-05) at a 1:10,000 dilution in blocking solution, 100μl/well for 1 hour at room temperature. Plates were developed using 75μl/well Bionostics TMB substrate and incubated for approximately 10 minutes. The developing reaction was stopped using Bionostics Red Stop solution (25μl/well), and the optical density of the plates was read at 650nm.

GST-PAX2 Peptides - Relative Binding to P100 Fractions

After subtraction of the GST-peptide binding to plastic from P100 binding values, the binding of GST-PAX2 peptides were represented as a ratio of GST-HAX42 binding to P100, which was given the arbitrary value of 1.00. The following ratios were determined from binding to P100 of GST-peptides at a peptide concentration of 20μg/ml. Bold denotes positive binding to the P100 membrane fraction.

Table 27

GST-peptide	Value
GST-HAX42	**1.00**
GST-PAX2	**1.79**
GST-104	0.01
GST-105	-0.08
GST-106	**2.71**
GST-113	0.26
GST-114	0.17
GST-115	0.36
GST	0.48

Table 28

	GST-peptide Amino Acid Sequence
GST-PAX2	**STPPSREAYSRPYSVDSDSDTNAKHSSHNRRLRTRSRPN**
GST-104	STPPSREAYSRPYSVDSDSD
GST-105	STPPSREAYSRPYSVDSDSDTNAKHSSHN
GST-106	**TNAKHSSHNRRLRTRSRPN**
GST-113	TNAKHSSHN
GST-114	SSHNRRLRTRSRPN
GST-115	RRLRTRSRPN

<u>**PAX2 Peptides - Relative Binding to P100 Fractions**</u>

ZElan021, full length HAX42, was given the arbitrary value of 1.00 for binding to P100 at a given peptide concentration determined from the signal-to-noise ratio data. PAX2 and its derivatives are given as a ratio of HAX42 value to reflect their binding abilities to P100 membrane fractions derived from a Caco-2 cell line as shown in Table 29. Table 30 provides a line-up of the PAX2 peptides showing the positive binding peptides in boldface. The GST-PAX2 peptide and PAX2 peptide data agree, demonstrating that a binding motif is in the amino acid sequence TNAKHSSHNRRLRTR (GST-106 and ZElan033).

TABLE 29

PAX2 peptide	Binding value at 20μg/ml	Binding value at 20μg/ml	Binding value at 50μg/ml	Binding value at 50μg/ml	Binding value at 50μg/ml (Jackson Ab)	Binding value at 50μg/ml (Southern Ab)
ZElan018	-0.33	1.07	0.95	1.01		
ZElan032	1.43	2.87	0.95	1.06		
ZElan033	0.35	1.57	0.80	0.66		
ZElan035	0.12	0.43	0.81	0.77		
ZElan055	0.99	0.73	1.10	0.59		
ZElan056	0.00	0.16	0.21	0.21		
ZElan057	0.08		0.56	0.25		
ZElan058	0.05		0.47	0.16		
ZElan073	0.07		-0.11	0.49	0.66	0.49
ZElan074	0.06		0.82	0.52	0.71	0.48
ZElan075	0.13		0.52	0.38	0.47	0.32
ZElan076	0.08		1.00	0.41	0.60	0.42
ZElan077	0.20		0.76	0.54	0.73	0.52
ZElan078	0.11		0.87	0.69	0.68	0.47
ZElan079	0.31		0.97	0.68	0.83	0.53
ZElan080	0.23		0.84	0.45	0.67	0.38
ZElan081	0.01		0.89	0.47		
ZElan082	0.00		0.92	0.40		
ZElan083	0.43	0.63	1.03	0.88		
ZElan084	1.06	0.93	1.16	0.77		

Table 30

PAX2 Peptide	Amino acid sequence	SEQ ID NO:
ZElan018	H_2N-K(dns)STPPSREAYSRPYSVDSDSDTNAKHSSHNRRLRTRSRPNG -$CONH_2$	
ZElan032	H_2N-K(dns)TNAKHSSHNRRLRTRSRPN-$CONH_2$	
ZElan033	H_2N-K(dns)TNAKHSSHNRRLRTR-$CONH_2$	
ZElan034	H_2N-K(dns)SSHNRRLRTRSRPN-$CONH_2$	
ZElan035	H_2N-K(dns)SSHNRRLRTR-$CONH_2$	
ZElan055	H_2N-K(dns)TNAKHSSHN-$CONH_2$	
ZElan056	H_2N-K(dns)RRLRTRSRPN-$CONH_2$	
ZElan057	H_2N-K(dns)RRLRTRSR-$CONH_2$	
ZElan058	H_2N-K(dns)RRLRTR-$CONH_2$	
ZElan059	H_2N-K(dns)rrLrTrSrPN-$CONH_2$	
ZElan073	H_2N-K(dns)ASHNRRLRTR-$CONH_2$	
ZElan074	H_2N-K(dns)SAHNRRLRTR-$CONH_2$	
ZElan075	H_2N-K(dns)SSANRRLRTR-$CONH_2$	
ZElan076	H_2N-K(dns)SSHARRLRTR-$CONH_2$	
ZElan077	H_2N-K(dns)SSHNARLRTR-$CONH_2$	
ZElan078	H_2N-K(dns)SSHNRALRTR-$CONH_2$	
ZElan079	H_2N-K(dns)SSHNRRARTR-$CONH_2$	
ZElan080	H_2N-K(dns)SSHNRRLATR-$CONH_2$	
ZElan081	H_2N-K(dns)SSHNRRLRAR-$CONH_2$	
ZElan082	H_2N-K(dns)SSHNRRLRTA-$CONH_2$	
SCRAMBLED PAX2 PEPTIDES:		
ZElan083	H_2N-K(dns)GRNHDVVSSNTHKSYRSPRSASYPRLSNDRTDRTEPAPSS-$CONH_2$	
ZElan084	H_2N-K(dns)RNTRNKTSRLSANPHRSHR-$CONH_2$	

HAX42 Peptides - Relative Binding to P100 Fractions

ZElan021, full length HAX42, was given the arbitrary value of 1.00 for binding to P100 at a given peptide concentration determined from the signal-to-noise ratio data. HAX42 and its derivatives are given as a ratio of HAX42 value to reflect their binding abilities to P100 membrane fractions derived from a Caco-2 cell line as shown in Table 31. Table 32 provides a line-up of the HAX42 peptides showing the positive binding peptides in boldface. A core binding motif appears to lie in the amino acid sequence PGDYNCCGNCNSTG (ZElan091).

TABLE 31

HAX42 peptide	Binding value at 20μg/ml	Binding value at 50μg/ml	Binding value at 50μg/ml	Binding value at 25μg/ml	Binding value at 25μg/ml	Binding value at 25μg/ml
ZElan021	1.00	1.00	1.00	1.00	1.00	1.00
ZElan060	0.44	0.56	0.43			
ZElan061	0.20	0.60	0.38			
ZElan062	0.11	0.42	0.34			
ZElan065	0.00	0.54	0.30			
ZElan067	0.08	0.52	0.40			
ZElan070	0.59	0.97	0.39			
ZElan071	1.22	0.89	0.75			
ZElan072	0.83	0.61	0.88			
ZElan087				0.46	0.44	
ZElan088				2.21	1.41	1.63
ZElan089				0.55	0.44	0.49
ZElan090				2.06	1.54	2.16
ZElan091				2.02	1.37	1.20
ZElan092				1.41	1.90	0.91
ZElan093				1.88	1.37	1.33

Table 32

HAX42 Peptide	Amino acid sequence
ZElan021	**H_2N-K(dns)SDHALGTNLRSDNAKEPGDYNCCGNGNSTGRKVFNRRRPSAIPT-$CONH_2$**
ZElan060	**H_2N-K(dns)SDHALGTNLRSDNAKEPGDYNCCGNG-$CONH_2$**
ZElan061	H_2N-K(dns) GNGNSTGRKVFNRRRPSAIPT-$CONH_2$
ZElan062	H_2N-K(dns)SDHALGTNLRSDNAKEPG-$CONH_2$
ZElan065	H_2N-K(dns)RKVFNRRRPS-$CONH_2$
ZElan067	H_2N-K(dns)NRRRPS-$CONH_2$
ZElan070	**H_2N-K(dns)SDHALGTNLRSDNAKEPGDYNCCGNGNST-$CONH_2$**
ZElan071	**H_2N-K(dns)NLRSDNAKEPGDYNCCGNGNSTGRKVFNR-$CONH_2$**
ZElan072	**H_2N-K(dns)PGDYNCCGNGNSTGRKVFNRRRPSAIPT-$CONH_2$**
ZElan087	H_2N-K(dns)SDHALGTNLRSDNAKEPGDY-$CONH_2$
ZElan088	**H_2N-K(dns)SDNAKEPGDYNCCGNGNSTG-$CONH_2$**
ZElan089	H_2N-K(dns)SDHALGTNLRSDNAK-$CONH_2$ -$CONH_2$
ZElan090	**H_2N-K(dns)EPGDYNCCGNGNSTG**
ZElan091	**H_2N-K(dns)PGDYNCCGNGNSTG-$CONH_2$**
ZElan092	**H_2N-K(dns)PGDYNCCGNG-$CONH_2$**
ZElan093	**H_2N-K(dns)NCCGNGNSTG-$CONH_2$**

9. FORMULATIONS

General Method for Preparation of Coacervated Particles.

Solid particles containing a Therapeutic as defined herein are prepared using a coacervation method. The are particles are formed from a polymer and have a particle size of between about 10nm and 500 μm, most preferably 50 to 800 nm. In addition the particles contain targeting ligands which are incorporated into the particles using a number of methods.

The organic phase (B) polymer of the general method given above may be soluble, permeable, impermeable,

biodegradable or gastroretentive. The polymer may consist of a mixture of polymer or copolymers and may be a natural or synthetic polymer. Representative biodegradable polymers include without limitation polyglycolides; polylactides; poly(lactide-co-glycolides), including DL, L and D forms; copolyoxalates; polycaprolactone; polyesteramides; polyorthoesters; polyanhydrides; polyalkylcyanoacrylates; polyhydroxybutyrates; polyurethanes; albumin; casein; citosan derivatives; gelatin; acacia; celluloses; polysaccharides; alginic acid; polypeptides; and the like, copolymers thereof, mixtures thereof and stereoisomers thereof. Representative synthetic polymers include alkyl celluloses; hydroxalkyl celluloses; cellulose ethers; cellulose esters; nitrocelluloses; polymers of acrylic and methacrylic acids and esters thereof; dextrans; polyamides; polycarbonates; polyalkylenes; polyalkylene glycols; polyalkylene oxides; polyalkylene terephthalates; polyvinyl alcohols; polyvinyl ethers; polyvinyl esters; polyvinyl halides; poyvinylpyrrolidone; polysiloxanes and polyurethanes and co-polymers thereof.

Typically, particles are formed using the following general method:

An aqueous solution (A) of a polymer, surface active agent, surface stabilising or modifying agent or salt, or surfactant preferably a polyvinyl alcohol (PVA) or derivative with a % hydrolysis 50 - 100% and a molecular weight range 500 - 500,000, most preferably 80-100% hydrolysis and 10,000-150,000 molecular weight, is introduced into a vessel. The mixture (A) is stirred under low shear conditions at 10- 2000 rpm, preferably 100-600 rpm. The pH and/or ionic strength of this solution may be modified using salts, buffers or other modifying agents. The viscosity of this solution may be modified using polymers, salts, or other viscosity enhancing or modifying agents.

A polymer, preferably poly(lacide-co-glycolide), polylactide, polyglycolide or a combination thereof or in any enantiomeric form or a covalent conjugate of the these

polymers with a targeting ligand is dissolved in water miscible organic solvents to form organic phase (B). Most preferably, a combination of acetone and ethanol is used in a range of ratios from 0:100 acetone: ethanol to 100: 0 acetone: ethanol depending upon the polymer used.

Additional polymer(s), peptide(s) sugars, salts, natural/biological polymers or other agents may also be added to the organic phase (B) to modify the physical and chemical properties of the resultant particle product.

A drug or bioactive substance may be introduced into either the aqueous phase (A) or the organic phase (B). A targeting ligand may also be introduced into either the aqueous phase (A) or the organic phase (B) at this point.

The organic phase (B) is added into the stirred aqueous phase (A) at a continuous rate. The solvent is evaporated, preferably by a rise in temperature over ambient and/or the use of a vacuum pump. The particles are now present as a suspension (C). A targeting ligand may be introduced into the stirred suspension at this point.

A secondary layer of polymer(s), peptide(s) sugars, salts, natural/biological polymers or other agents may be deposited on to the pre-formed particulate core by any suitable method at this stage.

The particles (D) are then separated from the suspension (C) using standard colloidal separation techniques, preferably by centrifugation at high 'g' force, filtration, gel permeation chromatography, affinity chromatography or charge separation techniques. The supernatant is discarded and the particles (D) re-suspended in a washing solution (E) preferably water, salt solution, buffer or organic solvent(s). The particles (D) are separated from the washing liquid in a similar manner as previously described and re-washed, commonly twice. A targeting ligand may be dissolved in washing solution (E) at the final washing stage and may be used to wash the particles (D).

The particles may then be dried. Particles may then be further processed for example, tabletted, encapsulated or spray dried.

The release profile of the particles formed above may be varied from immediate to controlled or delayed release dependent upon the formulation used and/or desired.

Drug loading may be in the range 0-90% w/w. Targeting ligand loading may be in the range 0-90% w/w.

Specific examples include the following examples:

EXAMPLE 1: Peptide added at the final washing stage

Product: Bovine Insulin loaded nanoparticles

Aim: To prepare a 2g batch of insulin loaded nanoparticles at a theoretical loading of 50mg/g and with the peptide ZElan018 added.

Formulation Details

RG504H (Lot no. 250583)	2.0g
Acetone	45ml
Ethanol:	5ml
PVA (aq. 5%w/v)	400ml
Bovine Insulin (Lot no. 86H0674)	100mg
Peptide: PAX2 (ZElan018)	10mg/50ml dH_2O

Experimental details:

The 5% w/v PVA solution was prepared by heating water until near boiling point, adding PVA and stirring until cool. The organic phase was prepared by adding acetone, 45ml, and ethanol, 5ml, together. The polymer solution was prepared by adding RG504H, 2g, to the organic phase and stirring until dissolved. The IKA™ reactor vessel was set up, all seals greased and the temperature was set at 25°C. The PVA solution, 400ml, was added into the reactor vessel and stirred at 400 rpm.

Bovine insulin, 100mg, was added into the stirring PVA solution. Using clean tubing and a green needle, the polymer solution was slowly dripped in the stirring PVA solution with the peristaltic pump set at 40. The solvent was allowed to

evaporate by opening the ports and allowing the dispersion to stir overnight at 400 rpm.

The suspension was centrifuged in a Beckman Ultracentrifuge™ with swing-out rotor at 12,500 rpm, 4°C. The supernatant was decanted and discarded. The "cake" of particles was broken up and dH_2O (200mls) was added to wash the particles. The centrifugation and washing steps were repeated twice.

The peptide solution, (ZElan018, 10mg in 50ml dH_2O) was prepared and added to the particles for a final washing stage. The suspended particles were centrifuged as before. The supernatant liquid was decanted, the 'cake' broken up, and the particles were dried in the vacuum oven.

The particles were ground, placed in a securitainer and sent for analysis. The weight of particles recovered was 1.45g. A SEM showed discrete, reasonably spherical particles in the 300-500nm size range. The potency was 49.2mg/g (98.0% of label claim). Peptide loading was 2.42 μg/mg (48.4% of label claim).

EXAMPLE 2: Peptide added at the beginning of manufacture

Product: Bovine Insulin loaded nanoparticles

Aim: To prepare a 2g batch of insulin loaded nanoparticles at a theoretical loading of 50mg/g and with the peptide ZElan018 added at the beginning of manufacture.

Formulation Details

RG504H (Lot no. 250583)	2.0g
Acetone	45ml
Ethanol:	5ml
PVA(aq. 5%w/v)	400ml
Bovine Insulin (Lot no. 65H0640)	100mg
Peptide: PAX2 (ZElan018ii)	10mg

Experimental details:

The 5% w/v PVA solution was prepared by heating water until near boiling point, adding PVA and stirring until cool. The organic phase was prepared by adding acetone,

45ml, and ethanol, 5ml, together. The polymer solution was prepared by adding RG504H (polyactide-co-glycolide, Boehringer Ingelheim), 2g, to the organic phase prepared in step above and stirring until dissolved. The IKA™ reactor vessel was set up, all seals greased and the temperature was set at 25°C. The PVA solution, 400ml, was added into the reactor vessel and stirred at 400 rpm.

Bovine insulin, 100mg, was added into the stirring PVA solution. PAX2 (ZElan018ii, 10mg) was added to the stirring PVA solution. Using clean tubing and a green needle, the polymer solution was slowly dripped into the stirring PVA solution with the peristaltic pump set at 40. The solvent was allowed to evaporate by opening the ports and allowing the dispersion to stir overnight at 400 rpm. The suspension was centrifuged in a Beckman Ultracentrifuge™ with swing-out rotor at 12,500 rpm, 4°C. The supernatant was decanted and discarded.

The "cake" of particles was broken up and dH_2O (200ml) was added to wash the particles. The centrifugation and washing steps were repeated twice. The 'cake' was broken up and the particles were dried in the vacuum oven.

The particles were ground, placed in a securitainer and sent for analysis. The weight of the particles recovered was 1.6g. The potency was 47.3mg/g (94.6% of label claim). Peptide loading was 1.689μg/mg (33.8% of label claim).

EXAMPLE 3 Peptide added 1 hour before centrifugation

Product: Bovine Insulin loaded nanoparticles

Aim: To prepare a 1g batch of insulin loaded nanoparticles at a theoretical loading of 50mg/g and with the peptide ZElan018 added 1 hour before centrifugation.

Formulation Details

RG504H (Lot no. 250583)	1.0g
Acetone	22.5ml
Ethanol:	2.5ml
PVA(aq. 5%w/v)	200ml
Bovine Insulin (Lot no. 65H0640)	50mg

Peptide: PAX2 (ZElan018) 5mg

Experimental details:

The 5% w/v PVA solution was prepared by heating water until near boiling point, adding PVA and stirring until cool. The organic phase was prepared by adding acetone, 22.5ml, and ethanol, 2.5ml, together. The polymer solution was prepared by adding RG504H, 1g, to the organic phase prepared above and stirring until dissolved. The IKA™ reactor vessel was set up, all seals greased and the temperature was set at 25°C. The PVA solution, 200ml, was added into the reactor vessel and stirred at 400 rpm.

Bovine insulin, 50mg, was added into the stirring PVA solution. Using clean tubing and a green needle, the polymer solution was slowly dripped in the stirring PVA solution with the peristaltic pump set at 40. The solvent was allowed to evaporate by opening the ports and allowing the dispersion to stir overnight at 400 rpm.

PAX2 (ZElan018 5mg) was added to the stirring particle suspension. After 1 hr, the suspension was centrifuged in a Beckman Ultracentrifuge™ with swing-out rotor at 12,500 rpm, 4°C. The supernatant was decanted and discarded. The "cake" of particles was broken up and dH_2O (200ml) was added to wash the particles. The centrifugation and washing steps were repeated twice.

The 'cake' was broken up and the particles were dried in the vacuum oven. The particles were ground, placed in a securitainer and sent for analysis. Potency was 20.75mg/g (41.5% of label claim). Peptide loading was 1.256μg/mg (25.12 % of label claim).

EXAMPLE 4: Leuprolide acetate loaded nanoparticles

Aim: To prepare a 3g batch of leuprolide-acetate loaded nanoparticles at a theoretical loading of 20mg/g and with the peptide ZElan024 added.

Formulation Details

RG504H (Lot no. 271077) 3.0g

Acetone	67.5ml
Ethanol:	7.5ml
PVA(aq. 5%w/v)	600ml
Leuprolide acetate (Lot no. V14094)	60mg
Peptide: P31 (ZElan024)	15mg/50ml dH_2O

Experimental details:

The PVA solution was prepared and the organic phase was prepared by adding acetone, 67.5ml, and ethanol, 7.5ml, together. The polymer solution was prepared by adding RG504H, 3g, to the organic phase prepared above and stirring until dissolved. The IKA™ reactor vessel was set up, all seals greased and the temperature was set at 25°C. The PVA solution, 600ml, was added into the reactor vessel and stirred at 400 rpm.

Leuprolide acetate, 60mg, was added into the stirring PVA solution. Using clean tubing and a green needle, the polymer solution, was slowly dripped in the stirring PVA solution with the peristaltic pump set at 40. The solvent was allowed to evaporate by opening the ports and allowing the dispersion to stir overnight at 400 rpm. The suspension was centrifuged in a Beckman Ultracentrifuge™ with swing-out rotor at 15,000 rpm, 4°C. The supernatant was decanted and retained for analysis.

The "cake" of particles was broken up and dH_2O 200ml) was added to wash the particles. The centrifugation and washing steps were repeated twice.

The peptide solution (P31 (SEQ ID NO:43), 15mg in 50ml dH_2O) was prepared and added to the particles for a final washing stage. The suspended particles were centrifuged as before. The supernatant liquid was decanted, and the particles were dried in the vacuum oven.

The particles were ground, placed in a securitainer and sent for analysis. The weight of particles recovered was 1.87g. SEM showed discrete, reasonably spherical particles in the 300-500nm size range. The potency was 4.7mg/g (23.4% of label claim). Peptide loading was 1.76μg/mg.

EXAMPLE 5: Peptide added by 'spiking' polymer phase with polymer-peptide conjugate

Product: Bovine Insulin loaded nanoparticles

Aim: To prepare a 3g batch of insulin loaded nanoparticles at a theoretical loading of 50mg/g and with the polymer-peptide conjugate PLGA-ZElan019 added.

Formulation Details

RG504H (Lot no. 271077)	2.85g
RG504H-ZElan019 conjugate (5PAX5-conjugate)	0.15g
Acetone	67.5ml
Ethanol:	7.5ml
PVA(aq. 5%w/v)	600ml
Bovine Insulin(Lot no. 86H0674)	150mg

Experimental details:

The 5% w/v PVA solution was prepared by heating water until near boiling point, adding PVA and stirring until cool. The organic phase was prepared by adding acetone, 67.5ml, and ethanol, 7.5ml, together. The polymer solution was prepared by adding RG504H and the polymer-peptide conjugate to the organic phase and stirring until dissolved.

The IKA™ reactor vessel was set up, all seals greased and the temperature was set at 25°C. The PVA solution, 400ml, was added into the reactor vessel and stirred at 400 rpm.

Bovine insulin, 100mg, was added into the stirring PVA solution. Using clean tubing and a green needle, the polymer solution, was slowly dripped in the stirring PVA solution with the peristaltic pump set at 40. The solvent was allowed to evaporate by opening the ports and allowing the dispersion to stir overnight at 400 rpm.

The suspension was centrifuged in a Beckman Ultracentrifuge™ with swing-out rotor at 12,500 rpm, 4°C. The supernatant was decanted and discarded. The "cake" of particles was broken up and dH_2O (200ml) was added to wash the

particles. The centrifugation washing step was repeated twice.

The 'cake' was broken up and the particles were dried in the vacuum oven. The particles were ground, placed in a securitainer and sent for analysis. The weight of particles recovered was 2.8g. The potency was 53.1mg/g 106.2% of label claim). Peptide loading was 4.02 μg/mg (80.4% of label claim).

10. ANIMAL STUDIES

Study 1

An open-loop study in which the test solution was injected directly into the ileum was done. Wistar rats (300-350g) were fasted for 4 hours and anaesthetized by intramuscular administration 15 to 20 minutes prior to administration of the test solution with a solution of ketamine [0.525 ml of ketamine (100 mg/ml) and 0.875 ml of acepromazine maleate-BP ACP (2mg/ml)]. The rats were then injected with a test solution (injection volume: 1.5ml PBS) intra-duodenally at 2-3 cm below the pyloris. The test solution contained either PLGA particles manufactured according to the coacervation procedure given above with or without targeting peptides or by the "spiked" method given above. Insulin (fast-acting bovine; 28.1 iu/mg) was incorporated in the particles at 5% drug loading for a total of 100iu insulin (70 mg particles) or 300iu insulin (210 mg particles). Blood glucose values for the rats were measured using a Glucometer™ (Bayer; 0.1 to 33.3 m/mol/L); plasma insulin values were measured using a Phadeseph RIA Kit™ (Upjohn Pharmacia; 3 to 240 μU/ml-assayed in duplicate). Systemic and portal blood was sampled.

Study groups included animals receiving test solutions containing particles coated with the following peptides shown in Table 33.

Table 33

Study Group	Receptor	Peptide
I	hSI	SNi10
		SNi34
II	hPEPT1	P31
		5PAX5
III	HPT1	PAX2
		HAX42
IV	D2H	DCX8
		DCX11
V ("spiked")	hPEPT1	P31-PLGA conjugate
		5PAX5-PLGA conjugate

Control groups included: 1) PBS control (1.5ml) Open-Loop; 2) Insulin solution (1iu/0.2ml) subcutaneous; 3) Insulin particles - no peptide (1iu/0.2ml) subcutaneous; 4) Insulin particles/all 8 peptides mix (1iu/0.2ml) subcutaneous; 5) Insulin loaded particles/peptide control (scrambled 5PAX5) (100iu/1.5ml) Open-Loop; 6) Insulin loaded particles/peptide control (scrambled 5PAX5) (300iu/1.5ml) Open-Loop; 7) Control particles (insulin-free)/all 8 peptide mix (equivalent 100iu/1.5ml) Open-Loop; and 8) Control particles (insulin-free)/all 8 peptide mix (equivalent 300iu/1.5ml) Open-Loop.

The following describes the pharmacokinetics for 300iu-loading:

Target Receptor	F%*	Fold-increase**	Stat. Sig.**
HPT1	10.37	17.0	<0.001
Spiked hPEPT1	4.94	7.5	0.005
PAX2 scrambled	3.50	3.6	NS
Mix-8	2.00	2.0	NS
hPEPT1	1.60	1.5	NS
D2H	1.57	1.4	NS
hSI	0.54	0.9	NS

* based on area under the curve (AUC) (1-4h), base-line adjusted, relative to subcutaneous insulin solution 1iu
** Fold increase in AUC compared to insulin particles: 300iu

Figures 17A and 17B show the systemic blood glucose and insulin levels following intestinal administration of control (PBS); insulin solution; insulin particles; all 8

peptides mix particles and study group peptide-particles (100iu). Figures 18A and 18B show the systemic blood glucose and insulin levels following intestinal administration of control (PBS); insulin solution; insulin particles and study group peptide-particles (300iu).

HPT1 targeted peptide coated particles provided the most potent enhancement of the delivery of insulin over subcutaneous injection of insulin followed by hPEPT1 spiked > PAX2 scrambled > mix-8 > hPEPT1 > D2H > uncoated particles > hSI > solution. In a repeat study, the uncoated particles containing insulin gave similar profiles but the HPT1-peptide targeted particles gave a reduced profile (3-fold). The insulin-free PLGA particles and the all-8 mix particles did not show an effect on the basal insulin or glucose levels. The HPT1 targeting particles, the PEPT1 spiked, targeting particles, and the PEPT1 targeting particles also reduced blood glucose levels indicative that the insulin delivered was bioactive. The other targeting particles were also shown to reduce blood glucose levels although not to the same extent as the HPT1 and PEPT1 spiked particles. No histological differences were observed in the small intestine for any of the formulations evaluated.

Study 2

A second open-loop study, similar to study 1 above, was undertaken with the following treatment groups as shown in Table 34.

Table 34

Group Number	Dose Insulin (iu)	Description
1		PBS control
2a	1	subcutaneous, bovine insulin
2b	2	subcutaneous, bovine insulin
2c	3	subcutaneous, bovine insulin
2d	4	subcutaneous, bovine insulin
2e	10	subcutaneous, bovine insulin

2f	20	subcutaneous, bovine insulin
2g	4	subcutaneous, human insulin
3	300	uncoated insulin particles
4	100	HAX42/PAX2 with 300 iu particle loading
5	300	HAX42/PAX2 (40mer) particles
6	300	HAX42 (40mer) particles
7	300	HAX42 particles + 10-fold excess free HAX42 (40mer)
8	300	PAX2 (40mer) particles
9	300	PAX2 freeze-dried (40mer) particles
10	300	PAX2 scrambled particles III (40mer)
11	300	PAX2 scrambled particles IV (19mer)
12	300	5PAX5/P31 (40mer) particles
13	300	P31 (40mer) particles
14	300	5PAX5 (40mer) particles
15	300	HAX42 (27mer) particles
16	300	PAX2 (20mer) particles
17	300	P31 (20mer) particles
18	300	PAX2 (15mer) particles
19	300	P31 (15mer) particles
20	300	P31 D-form I(5 D-arginine)(16mer) particles
21	300	P31 D-form II(2 D-arginine)(16mer) particles
22	300	HAX42 (10mer)

Availability of insulin following administration was assessed relative to a 1 and 20iu subcutaneous dose because the response to increasing subcutaneous doses of bovine insulin does not increase linearly over the range of 1 to 20iu. Data up to three hours post-dosing was available for most animals. Therefore, availability was first assessed using individual AUC(0-3h) data estimated from baseline-subtracted data for which data up to 3 hours was available. This approach may lead to an underestimation of the availability as some animals that gave a high response often did not survive for 3 hours and, therefore, were excluded from the analyses. In an attempt to capture as much of these high responses observed at the earlier timepoints as possible, the mean baseline-subtracted plasma concentration

data was used to estimate an AUC for each group. Table 35 shows the results based on this second approach (AUC(0-3h) calculated from the mean plasma concentration data).

Table 35

Group	Dose iu	Mean $AUC_{(0-3h)}$	F vs. 1 iu	F vs. 20 iu
1	0	2.14		
2a	1	875.27	100.00	28.86
2b	2	2439.36	139.35	40.22
2c	3	3671.44	139.82	40.36
2d	4	6912.18	197.43	56.98
2e	10	27224.41	311.04	89.77
2f	20	60651.28	346.47	100.00
2g	4	14255.49	407.17	117.52
3	300	10677.78	4.07	1.17
3 -Rat43	300	4645.06	1.77	0.51
4	100	3527.18	4.03	1.16
5	300	27112.26	10.33	2.98
6	300	33091.68	12.60	3.64
7	300	9303.09	3.54	1.02
8	300	34241.83	13.04	3.76
9	300	10968.83	4.18	1.21
10	300	27692.78	10.55	3.04
11	300	3004.29	1.14	0.33
12	300	18852.61	7.18	2.07
13	300	20278.43	7.72	2.23
14	300	17400.38	6.63	1.91
15	300	16775.69	6.39	1.84
16	300	14217.47	5.41	1.56
17	300	8197.97	3.12	0.90
18	300	25050.59	9.54	2.75
19	300	7927.96	3.02	0.87
20	300	21519.57	8.20	2.37
21	300	6322.41	2.41	0.69
22	300	12553.01	4.78	1.38

The data for group 3 (uncoated insulin particles) are expressed with and without Rat 43. This animal had an atypically high response to these uncoated particles and, therefore, may have biased the data for this group.

This data shows that a combination of peptide-coated particles (HAX42/PAX2 or 5PAX5/P31) shows no greater availability than particles coated with the individual peptides. Further, peptide-coated particles have a greater availability than uncoated peptides. Scrambling the 40mer

PAX2 peptide did not result in a loss of bioavailability. Scrambling the PAX2 peptide and reducing the size to 19mer resulted in a loss of bioavailability although this loss may be attributed in part to the reduction in peptide size. Reducing peptide size resulted in loss of bioavailability. The D-form of P31 (ZElan053) had increased bioavailability possibly due to greater resistance to peptide breakdown. A competitive excess of peptide resulted in a loss of bioavailability, and freeze drying caused a loss in bioavailability. By way of example, measurement of blood glucose levels showed that the HPT1 and hPEPT1 targeting particles incorporating HAX42, PAX2, P31 (SEQ ID NO:43), and P31 D-form (ZElan053) reduced blood glucose levels indicating that the insulin delivered was bioactive.

In further studies, insulin was recovered from the targeting particles following particle formation by dissolution and analyzed by electrophoresis in non-denaturing sodum dodecyl sulfate (SDS) polyacrylamide gel electrophoresis (PAGE). The analysis of the insulin by non-denaturing SDS-PAGE and also by western blot transferred to membranes and subsequent screening with an antibody to insulin, indicated that the insulin was intact, with no evidence of degradation, dimerization, or aggregation during the process of particle formation.

Study 3

An intraduodenal open loop model study was carried out on Wistar rats (300-350g). Group 1 was administered leuprolide acetate (12.5 μg) subcutaneously. Group 2 was administered intraduodenally uncoated leuprolide acetate particles (600 μg, 1.5 ml). Group 3 was intraduodenally administered leuprolide acetate particles coated with PAX2 (600 μg; 1.5 ml). Group 4 was administered intraduodenally leuprolide acetate particles coated with P31 (SEQ ID NO:43) (600 μg, 1.5 ml). Figure 19 shows the leuprolide plasma concentration following administration to these four groups. Both the P31 (SEQ ID NO:43) and the PAX2 coated leuprolide

particles administered intraduodenally provided enhanced plasma levels of leuprolide relative to subcutaneous injection.

Homologies of GIT transport-binding peptides to known proteins are shown in Figures 20, 21A-F, and 22 A-D.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

SEQUENCE LISTING

(1) GENERAL INFORMATION

(i) APPLICANTS: CYTOGEN CORPORATION and ÉLAN CORPORATION, plc

(ii) TITLE OF THE INVENTION: RANDOM PEPTIDES THAT BIND TO GASTRO-INTESTINAL TRACT (GIT) TRANSPORT RECEPTORS AND RELATED METHODS

(iii) NUMBER OF SEQUENCES: 265

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Pennie & Edmonds LLP
(B) STREET: 1155 Avenue of the Americas
(C) CITY: New York
(D) STATE: New York
(E) COUNTRY: USA
(F) ZIP: 10036

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Diskette
(B) COMPUTER: IBM Compatible
(C) OPERATING SYSTEM: DOS
(D) SOFTWARE: FastSEQ Version 2.0

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Misrock, S. Leslie
(B) REGISTRATION NUMBER: 18,872
(C) REFERENCE/DOCKET NUMBER: 1101-209-228

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 212-790-9090
(B) TELEFAX: 212-869-9741
(C) TELEX: 66141 PENNIE

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
Arg Ser Gly Ala Tyr Glu Ser Pro Asp Gly Arg Gly Gly Arg Ser Tyr
 1               5                  10                  15
Val Gly Gly Gly Gly Gly Cys Gly Asn Ile Gly Arg Lys His Asn Leu
            20                  25                  30
Trp Gly Leu Arg Thr Ala Ser Pro Ala Cys Trp Asp
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Ser Pro Arg Ser Phe Trp Pro Val Val Ser Arg His Glu Ser Phe Gly
 1               5                  10                  15
Ile Ser Asn Tyr Leu Gly Cys Gly Tyr Arg Thr Cys Ile Ser Gly Thr
            20                  25                  30
Met Thr Lys Ser Ser Pro Ile Tyr Pro Arg His Ser
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
Ser Ser Ser Ser Asp Trp Gly Gly Val Pro Gly Lys Val Val Arg Glu
 1               5                  10                  15
Arg Phe Lys Gly Arg Gly Cys Gly Ile Ser Ile Thr Ser Val Leu Thr
            20                  25                  30
Gly Lys Pro Asn Pro Cys Pro Glu Pro Lys Ala Ala
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
Arg Val Gly Gln Cys Thr Asp Ser Asp Val Arg Arg Pro Trp Ala Arg
 1               5                  10                  15
Ser Cys Ala His Gln Gly Cys Gly Ala Gly Thr Arg Asn Ser His Gly
            20                  25                  30
Cys Ile Thr Arg Pro Leu Arg Gln Ala Ser Ala His
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
Ser His Ser Gly Gly Met Asn Arg Ala Tyr Gly Asp Val Phe Arg Glu
 1               5                  10                  15
Leu Arg Asp Arg Trp Asn Ala Thr Ser His His Thr Arg Pro Thr Pro
            20                  25                  30
Gln Leu Pro Arg Gly Pro Asn
        35
```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 41 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```
Ser Pro Cys Gly Gly Ser Trp Gly Arg Phe Met Gln Gly Gly Leu Phe
 1               5                  10                  15
Gly Gly Arg Thr Asp Gly Cys Gly Ala His Arg Asn Arg Thr Ser Ala
            20                  25                  30
Ser Leu Glu Pro Pro Ser Ser Asp Tyr
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```
Arg Gly Ala Ala Asp Gln Arg Arg Gly Trp Ser Glu Asn Leu Gly Leu
 1               5                  10                  15
Pro Arg Val Gly Trp Asp Ala Ile Ala His Asn Ser Tyr Thr Phe Thr
            20                  25                  30
Ser Arg Arg Pro Arg Pro Pro
        35
```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```
Ser Gly Gly Glu Val Ser Ser Trp Gly Arg Val Asn Asp Leu Cys Ala
 1               5                  10                  15
Arg Val Ser Trp Thr Gly Cys Gly Thr Ala Arg Ser Ala Arg Thr Asp
            20                  25                  30
Asn Lys Gly Phe Leu Pro Lys His Ser Ser Leu Arg
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```
Ser Asp Ser Asp Gly Asp His Tyr Gly Leu Arg Gly Gly Val Arg Cys
 1               5                  10                  15
Ser Leu Arg Asp Arg Gly Cys Gly Leu Ala Leu Ser Thr Val His Ala
            20                  25                  30
Gly Pro Pro Ser Phe Tyr Pro Lys Leu Ser Ser Pro
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
Arg Ser Leu Gly Asn Tyr Gly Val Thr Gly Thr Val Asp Val Thr Val
 1               5                  10                  15
Leu Pro Met Pro Gly His Ala Asn His Leu Gly Val Ser Ser Ala Ser
            20                  25                  30
Ser Ser Asp Pro Pro Arg Arg
        35
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
Arg Thr Thr Thr Ala Lys Gly Cys Leu Leu Gly Ser Phe Gly Val Leu
 1               5                  10                  15
Ser Gly Cys Ser Phe Thr Pro Thr Ser Pro Pro Pro His Leu Gly Tyr
            20                  25                  30
Pro Pro His Ser Val Asn
        35
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
Ser Pro Lys Leu Ser Ser Val Gly Val Met Thr Lys Val Thr Glu Leu
 1               5                  10                  15
Pro Thr Glu Gly Pro Asn Ala Ile Ser Ile Pro Ile Ser Ala Thr Leu
            20                  25                  30
Gly Pro Arg Asn Pro Leu Arg
        35
```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```
Arg Trp Cys Gly Ala Glu Leu Cys Asn Ser Val Thr Lys Lys Phe Arg
 1               5                  10                  15
Pro Gly Trp Arg Asp His Ala Asn Pro Ser Thr His His Arg Thr Pro
            20                  25                  30
Pro Pro Ser Gln Ser Ser Pro
        35
```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
Arg Trp Cys Gly Ala Asp Asp Pro Cys Gly Ala Ser Arg Trp Arg Gly
 1               5                  10                  15
Gly Asn Ser Leu Phe Gly Cys Gly Leu Arg Cys Ser Ala Ala Gln Ser
            20                  25                  30
Thr Pro Ser Gly Arg Ile His Ser Thr Ser Thr Ser
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
Ser Lys Ser Gly Glu Gly Gly Asp Ser Ser Arg Gly Glu Thr Gly Trp
 1               5                  10                  15
Ala Arg Val Arg Ser His Ala Met Thr Ala Gly Arg Phe Arg Trp Tyr
            20                  25                  30
Asn Gln Leu Pro Ser Asp Arg
        35
```

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
Arg Ser Ser Ala Asn Asn Cys Glu Trp Lys Ser Asp Trp Met Arg Arg
 1               5                  10                  15
Ala Cys Ile Ala Arg Tyr Ala Asn Ser Ser Gly Pro Ala Arg Ala Val
            20                  25                  30
Asp Thr Lys Ala Ala Pro
        35
```

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
Ser Lys Trp Ser Trp Ser Ser Arg Trp Gly Ser Pro Gln Asp Lys Val
 1               5                  10                  15
Glu Lys Thr Arg Ala Gly Cys Gly Gly Ser Pro Ser Ser Thr Asn Cys
            20                  25                  30
His Pro Tyr Thr Phe Ala Pro Pro Pro Gln Ala Gly
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
Ser Gly Phe Trp Glu Phe Ser Arg Gly Leu Trp Asp Gly Glu Asn Arg
 1               5                  10                  15
Lys Ser Val Arg Ser Gly Cys Gly Phe Arg Gly Ser Ser Ala Gln Gly
            20                  25                  30
Pro Cys Pro Val Thr Pro Ala Thr Ile Asp Lys His
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
Ser Glu Ser Gly Arg Cys Arg Ser Val Ser Arg Trp Met Thr Thr Trp
 1               5                  10                  15
Gln Thr Gln Lys Gly Gly Cys Gly Ser Asn Val Ser Arg Gly Ser Pro
            20                  25                  30
Leu Asp Pro Ser His Gln Thr Gly His Ala Thr Thr
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
Arg Glu Trp Arg Phe Ala Gly Pro Pro Leu Asp Leu Trp Ala Gly Pro
 1               5                  10                  15
Ser Leu Pro Ser Phe Asn Ala Ser Ser His Pro Arg Ala Leu Arg Thr
            20                  25                  30
Tyr Trp Ser Gln Arg Pro Arg
        35
```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```
Arg Met Glu Asp Ile Lys Asn Ser Gly Trp Arg Asp Ser Cys Arg Trp
 1               5                  10                  15
Gly Asp Leu Arg Pro Gly Cys Gly Ser Arg Gln Trp Tyr Pro Ser Asn
            20                  25                  30
Met Arg Ser Ser Arg Asp Tyr Pro Ala Gly Gly His
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```
Ser His Pro Trp Tyr Arg His Trp Asn His Gly Asp Phe Ser Gly Ser
 1               5                  10                  15
Gly Gln Ser Arg His Thr Pro Pro Glu Ser Pro His Pro Gly Arg Pro
            20                  25                  30
Asn Ala Thr Ile
        35
```

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```
Arg Tyr Lys His Asp Ile Gly Cys Asp Ala Gly Val Asp Lys Lys Ser
 1               5                  10                  15
Ser Ser Val Arg Gly Gly Cys Gly Ala His Ser Ser Pro Pro Arg Ala
            20                  25                  30
Gly Arg Gly Pro Arg Gly Thr Met Val Ser Arg Leu
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```
Ser Gln Gly Ser Lys Gln Cys Met Gln Tyr Arg Thr Gly Arg Leu Thr
 1               5                  10                  15
Val Gly Ser Glu Tyr Gly Cys Gly Met Asn Pro Ala Arg His Ala Thr
            20                  25                  30
Pro Ala Tyr Pro Ala Arg Leu Leu Pro Arg Tyr Arg
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
Ser Gly Arg Thr Thr Ser Glu Ile Ser Gly Leu Trp Gly Trp Gly Asp
 1               5                  10                  15
Asp Arg Ser Gly Tyr Gly Trp Gly Asn Thr Leu Arg Pro Asn Tyr Ile
            20                  25                  30
Pro Tyr Arg Gln Ala Thr Asn Arg His Arg Tyr Thr
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```
Arg Trp Asn Trp Thr Val Leu Pro Ala Thr Gly Gly His Tyr Trp Thr
 1               5                  10                  15
Arg Ser Thr Asp Tyr His Ala Ile Asn Asn His Arg Pro Ser Ile Pro
            20                  25                  30
His Gln His Pro Thr Pro Ile
        35
```

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```
Ser Trp Ser Ser Trp Asn Trp Ser Ser Lys Thr Thr Arg Leu Gly Asp
 1               5                  10                  15
Arg Ala Thr Arg Glu Gly Cys Gly Pro Ser Gln Ser Asp Gly Cys Pro
            20                  25                  30
Tyr Asn Gly Arg Leu Thr Thr Val Lys Pro Arg Thr
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Ser Gly Ser Leu Asn Ala Trp Gln Pro Arg Ser Trp Val Gly Gly Ala
 1               5                  10                  15
Phe Arg Ser His Ala Asn Asn Asn Leu Asn Pro Lys Pro Thr Met Val
            20                  25                  30
Thr Arg His Pro Thr
        35
```

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```
Arg Tyr Ser Gly Leu Ser Pro Arg Asp Asn Gly Pro Ala Cys Ser Gln
 1               5                  10                  15
Glu Ala Thr Leu Glu Gly Cys Gly Ala Gln Arg Leu Met Ser Thr Arg
            20                  25                  30
Arg Lys Gly Arg Asn Ser Arg Pro Gly Trp Thr Leu
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```
Ser Val Gly Asn Asp Lys Thr Ser Arg Pro Val Ser Phe Tyr Gly Arg
 1               5                  10                  15
Val Ser Asp Leu Trp Asn Ala Ser Leu Met Pro Lys Arg Thr Pro Ser
            20                  25                  30
Ser Lys Arg His Asp Asp Gly
        35
```

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
Arg Trp Pro Ser Val Gly Tyr Lys Gly Asn Gly Ser Asp Thr Ile Asp
 1               5                  10                  15
Val His Ser Asn Asp Ala Ser Thr Lys Arg Ser Leu Ile Tyr Asn His
            20                  25                  30
Arg Arg Pro Leu Phe Pro
        35
```

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```
Arg Thr Phe Glu Asn Asp Gly Leu Gly Val Gly Arg Ser Ile Gln Lys
 1               5                  10                  15
Lys Ser Asp Arg Trp Tyr Ala Ser His Asn Ile Arg Ser His Phe Ala
            20                  25                  30
Ser Met Ser Pro Ala Gly Lys
        35
```

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Ser Tyr Cys Arg Val Lys Gly Gly Gly Glu Gly Gly His Thr Asp Ser
1 5 10 15
Asn Leu Ala Arg Ser Gly Cys Gly Lys Val Ala Arg Thr Ser Arg Leu
20 25 30
Gln His Ile Asn Pro Arg Ala Thr Pro Pro Ser Arg
35 40

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Ser Trp Thr Arg Trp Gly Lys His Thr His Gly Gly Phe Val Asn Lys
1 5 10 15
Ser Pro Pro Gly Lys Asn Ala Thr Ser Pro Tyr Thr Asp Ala Gln Leu
20 25 30
Pro Ser Asp Gln Gly Pro Pro
35

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Ser Gln Val Asp Ser Phe Arg Asn Ser Phe Arg Trp Tyr Glu Pro Ser
1 5 10 15
Arg Ala Leu Cys His Gly Cys Gly Lys Arg Asp Thr Ser Thr Thr Arg
20 25 30
Ile His Asn Ser Pro Ser Asp Ser Tyr Pro Thr Arg
35 40

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Ser Phe Leu Arg Phe Gln Ser Pro Arg Phe Glu Asp Tyr Ser Arg Thr
1 5 10 15
Ile Ser Arg Leu Arg Asn Ala Thr Asn Pro Ser Asn Val Ser Asp Ala
20 25 30
His Asn Asn Arg Ala Leu Ala
35

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

```
Arg Ser Ile Thr Asp Gly Gly Ile Asn Glu Val Asp Leu Ser Ser Val
 1               5                  10                  15
Ser Asn Val Leu Glu Asn Ala Asn Ser His Arg Ala Tyr Arg Lys His
            20                  25                  30
Arg Pro Thr Leu Lys Arg Pro
        35
```

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

```
Ser Ser Lys Val Ser Ser Pro Arg Asp Pro Thr Val Pro Arg Lys Gly
 1               5                  10                  15
Gly Asn Val Asp Tyr Gly Cys Gly His Arg Ser Ser Ala Arg Met Pro
            20                  25                  30
Thr Ser Ala Leu Ser Ser Ile Thr Lys Cys Tyr Thr
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

```
Arg Ala Ser Thr Gln Gly Gly Arg Gly Val Ala Pro Glu Phe Gly Ala
 1               5                  10                  15
Ser Val Leu Gly Arg Gly Cys Gly Ser Ala Thr Tyr Tyr Thr Asn Ser
            20                  25                  30
Thr Ser Cys Lys Asp Ala Met Gly His Asn Tyr Ser
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Arg Trp Cys Glu Lys His Lys Phe Thr Ala Ala Arg Cys Ser Ala Gly
1 5 10 15
Ala Gly Phe Glu Arg Asp Ala Ser Arg Pro Pro Gln Pro Ala His Arg
20 25 30
Asp Asn Thr Asn Arg Asn Ala
35

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Ser Phe Gln Val Tyr Pro Asp His Gly Leu Glu Arg His Ala Leu Asp
1 5 10 15
Gly Thr Gly Pro Leu Tyr Ala Met Pro Gly Arg Trp Ile Arg Ala Arg
20 25 30
Pro Gln Asn Arg Asp Arg Gln
35

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Ser Arg Cys Thr Asp Asn Glu Gln Cys Pro Asp Thr Gly Thr Arg Ser
1 5 10 15
Arg Ser Val Ser Asn Ala Arg Tyr Phe Ser Ser Arg Leu Leu Lys Thr
20 25 30
His Ala Pro His Arg Pro
35

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Ser Ala Arg Asp Ser Gly Pro Ala Glu Asp Gly Ser Arg Ala Val Arg
1 5 10 15
Leu Asn Gly Val Glu Asn Ala Asn Thr Arg Lys Ser Ser Arg Ser Asn
20 25 30
Pro Arg Gly Arg Arg His Pro
35

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

```
Ser Ser Ala Asp Ala Glu Lys Cys Ala Gly Ser Leu Leu Trp Trp Gly
 1               5                  10                  15
Arg Gln Asn Asn Ser Gly Cys Gly Ser Pro Thr Lys Lys His Leu Lys
            20                  25                  30
His Arg Asn Arg Ser Gln Thr Ser Ser Ser Ser His
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

```
Arg Pro Lys Asn Val Ala Asp Ala Tyr Ser Ser Gln Asp Gly Ala Ala
 1               5                  10                  15
Ala Glu Glu Thr Ser His Ala Ser Asn Ala Ala Arg Lys Ser Pro Lys
            20                  25                  30
His Lys Pro Leu Arg Arg Pro
        35
```

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

```
Arg Gly Ser Thr Gly Thr Ala Gly Gly Glu Arg Ser Gly Val Leu Asn
 1               5                  10                  15
Leu His Thr Arg Asp Asn Ala Ser Gly Ser Gly Phe Lys Pro Trp Tyr
            20                  25                  30
Pro Ser Asn Arg Gly His Lys
        35
```

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

```
Arg Trp Gly Trp Glu Arg Ser Pro Ser Asp Tyr Asp Ser Asp Met Asp
1               5                   10                  15
Leu Gly Ala Arg Arg Tyr Ala Thr Arg Thr His Arg Ala Pro Pro Arg
            20                  25                  30
Val Leu Lys Ala Pro Leu Pro
        35
```

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

```
Arg Gly Trp Lys Cys Glu Gly Ser Gln Ala Ala Tyr Gly Asp Lys Asp
1               5                   10                  15
Ile Gly Arg Ser Arg Gly Cys Gly Ser Ile Thr Lys Asn Asn Thr Asn
            20                  25                  30
His Ala His Pro Ser His Gly Ala Val Ala Lys Ile
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

```
Ser Arg Glu Glu Ala Asn Trp Asp Gly Tyr Lys Arg Glu Met Ser His
1               5                   10                  15
Arg Ser Arg Phe Trp Asp Ala Thr His Leu Ser Arg Pro Arg Arg Pro
            20                  25                  30
Ala Asn Ser Gly Asp Pro Asn
        35
```

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

```
Glu Trp Tyr Ser Trp Lys Arg Ser Ser Lys Ser Thr Gly Leu Gly Asp
1               5                   10                  15
Thr Ala Thr Arg Glu Gly Cys Gly Pro Ser Gln Ser Asp Gly Cys Pro
            20                  25                  30
Tyr Asn Gly Arg Leu Thr Thr Val Lys Pro Arg Lys
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

```
Arg Glu Phe Ala Glu Arg Arg Leu Trp Gly Cys Asp Asp Leu Ser Trp
 1               5                  10                  15
Arg Leu Asp Ala Glu Gly Cys Gly Pro Thr Pro Ser Asn Arg Ala Val
            20                  25                  30
Lys His Arg Lys Pro Arg Pro Arg Ser Pro Ala Leu
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

```
Ser Asp His Ala Leu Gly Thr Asn Leu Arg Ser Asp Asn Ala Lys Glu
 1               5                  10                  15
Pro Gly Asp Tyr Asn Cys Cys Gly Asn Gly Asn Ser Thr Gly Arg Lys
            20                  25                  30
Val Phe Asn Arg Arg Arg Pro Ser Ala Ile Pro Thr
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

```
Arg His Ile Ser Glu Tyr Ser Phe Ala Asn Ser His Leu Met Gly Gly
 1               5                  10                  15
Glu Ser Lys Arg Lys Gly Cys Gly Ile Asn Gly Ser Phe Ser Pro Thr
            20                  25                  30
Cys Pro Arg Ser Pro Thr Pro Ala Phe Arg Arg Thr
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Ser Arg Glu Ser Gly Met Trp Gly Ser Trp Trp Arg Gly His Arg Leu
1 5 10 15
Asn Ser Thr Gly Gly Asn Ala Asn Met Asn Ala Ser Leu Pro Pro Asp
20 25 30
Pro Pro Val Ser Thr Pro
35

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Ser Thr Pro Pro Ser Arg Glu Ala Tyr Ser Arg Pro Tyr Ser Val Asp
1 5 10 15
Ser Asp Ser Asp Thr Asn Ala Lys His Ser Ser His Asn Arg Arg Leu
20 25 30
Arg Thr Arg Ser Arg Pro Asn
35

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

TCTCACTCCT CGAGATCCGG CGCTTATGAG AGTCCGGATG GTCGGGGGGG TCGGAGCTAT 60
GTGGGGGGCG GGGGTGGNTG TGGTAACATT GGTCGGAAGC ATAACCTGTG GGGGCTGCGT 120
ACCGCGTCGC CGGCCTGCTG GGACTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA 177

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

TCTCACTCCT CGAGTCCTCG CTCTTTCTGG CCCGTTGTGT CCCGGCATGA GTCGTTTGGG 60
ATCTCTAACT ATTTGGGNTG TGGTTATCGT ACATGTATCT CCGGCACGAT GACTAAGTCT 120
AGCCCGATTT ACCCTCGGCA TTCGTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA 177

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

```
TCTCACTCCT CGAGTAGTAG CTCCGATTGG GGTGGTGTGC CTGGGAAGGT GGTTAGGGAG    60
CGCTTTAAGG GGCGCGGTTG TGGTATTTCC ATCACCTCCG TGCTCACTGG GAAGCCCAAT   120
CCGTGTCCGG AGCCTAAGGC GGCCTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA      177
```

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

```
TCTCACTCCT CGAGAGTTGG CCAGTGCACG GATTCTGATG TGCGGCGTCC TTGGGCCAGG    60
TCTTGCGCTC ATCAGGGTTG TGGTGCGGGC ACTCGCAACT CGCACGGCTG CATCACCCGT   120
CCTCTCCGCC AGGCTAGCGC TCATTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA      177
```

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

```
TCTCACTCCT CGAGCCACTC CGGTGGTATG AATAGGGCCT ACGGGGATGT GTTTAGGGAG    60
CTTCGTGATC GGTGGAACGC CACTTCCCAC CACACTCGCC CCACCCCTCA GCTCCCCCGT   120
GGGCCTAATT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA                      162
```

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 168 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

```
TCTCACTCCT CGAGTCCGTG CGGGGGGTCG TGGGGGCGTT TTATGCAGGG TGGCCTTTTC    60
GGCGGTAGGA CTGATGGTTG TGGTGCCCAT AGAAACCGCA CTTCTGCGTC GTTAGAGCCC   120
CCGAGCAGCG ACTACTCTAG AATCGAAGGT CGCGCTAGAC CTTCGAGA                168
```

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 135 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

```
TCTCACTCCT CGAGGGGCGC CGCCGATCAG CGGCGGGGGT GGTCCGAGAA CTTGGGGTTG     60
CCTAGGGTGG GGTGGGACGC CATCGCTCAC AATAGCTATA CGTTCACCTC GCGCCGCCCG    120
CGCCCCCCCT CTAGA                                                     135
```

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

```
TCTCACTCCT CGAGCGGTGG GGAGGTCAGC TCCTGGGGCC GCGTGAATGA CCTCTGCGCT     60
AGGGTGAGTT GGACTGGTTG TGGTACTGCT CGTTCCGCGC GTACCGACAA CAAAGGCTTT    120
CTTCCTAAGC ACTCGTCACT CCGCTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA       177
```

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

```
TCTCACTCCT CGAGTGATAG TGACGGGGAT CATTATGGGC TTCGGGGGGG GGTGCGTTGT     60
TCGCTTCGTG ATAGGGGTTG TGGTCTGGCC CTGTCCACCG TCCATGCTGG TCCCCCCTCT    120
TTTTACCCCA AGCTCTCCAG CCCCTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA       177
```

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

```
TCTCACTCCT CGAGGAGCTT GGGTAATTAT GGCGTCACCG GGACTGTGGA CGTGACGGTT     60
TTGCCCATGC CTGGCCACGC CAACCACCTT GGTGTCTCCT CCGCCTCTAG CTCTGATCCT    120
CCGCGGCGCT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA                       162
```

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 159 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

TCTCACTCCT CGAGAACTAC GACGGCTAAG GGGTGTCTTC TCGGAAGCTT CGGCGTTCTT 60
AGTGGGTGCT CATTTACGCC AACCTCTCCA CCGCCCCACC TAGGATACCC CCCCCACTCC 120
GTCAATTCTA GAATCGAAGG TCGCGCTAGA CCTTCGAGA 159

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

TCTCACTCCT CGAGCCCGAA GTTGTCCAGC GTGGGTGTTA TGACTAAGGT CACGGAGCTG 60
CCCACGGAGG GGCCTAACGC CATTAGTATT CCGATCTCCG CGACCCTCGG CCCGCGCAAC 120
CCGCTCCGCT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA 162

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

TCTCACTCCT CGAGGTGGTG CGGCGCTGAG CTGTGCAACT CGGTGACTAA GAAGTTTCGC 60
CCGGGCTGGC GGGATCACGC CAATCCCTCC ACCCATCATC GTACTCCCCC GCCCAGCCAG 120
TCCAGCCCTT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA 162

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 176 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

TCTCACTCCT CGAGGTGGTG CGGCGCTGAT GACCCGTGTG GTGCCAGTCG TTGGCGGGGG 60
GGCAACAGCT TGTTTGGTTG TGGTCTTCGT TGTAGTGCGG CGCAGAGCAC CCCGAGTGGC 120
AGGATCCATT CCACTTCGAC CAGCTCTAGA ATCGAAGGTG CGCTAGACCT TCGAGA 176

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

TCTCACTCCT CGAGTAAGTC CGGGGAGGGG GGTGACAGTA GCAGGGGCGA GACGGGCTGG 60
GCGAGGGTTC GGTCTCACGC CATGACTGCT GGCCGCTTTC GGTGGTACAA CCAGTTGCCC 120

TCTGATCGGT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA 162

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 159 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

TCTCACTCCT CGAGGTCGAG CGCCAATAAT TGCGAGTGGA AGTCTGATTG GATGCGCAGG 60
GCCTGTATTG CTCGTTACGC CAACAGTTCG GGCCCCGCCC GCGCCGTCGA CACTAAGGCC 120
GCGCCCTCTA GAATCGAAGG TCGCGCTAGA CCTTCGAGA 159

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

TCTCACTCCT CGAGTAAGTG GTCGTGGAGT TCGAGGTGGG GCTCCCCGCA GGATAAGGTT 60
GAGAAGACCA GGGCGGGTTG TGGTGGTAGT CCCAGCAGCA CCAATTGTCA CCCCTACACC 120
TTTGCCCCCC CCCCGCAAGC CGGCTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA 177

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

TCTCACTCCT CGAGTGGGTT CTGGGAGTTT AGCAGGGGGC TTTGGGATGG GGAGAACCGT 60
AAGAGTGTCC GGTCGGGTTG TGGTTTTCGT GGCTCCTCTG CTCAGGGCCC GTGTCCGGTC 120
ACGCCTGCCA CCATTGACAA ACACTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA 177

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

TCTCACTCCT CGAGTGAGAG CGGGCGGTGC CGTAGCGTGA GCCGGTGGAT GACGACGTGG 60
CAGACGCAGA AGGGCGGTTG TGGTTCCAAT GTTTCCCGCG GTTCGCCCCT CGACCCCTCT 120
CACCAGACCG GGCATGCCAC TACTTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA 177

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

```
TCTCACTCCT CGAGGGAGTG GAGGTTTGCC GGGCCGCCGT TGGACCTGTG GGCGGGTCCG    60
AGCTTGCCCT CTTTTAACGC CAGTTCCCAC CCTCGCGCCC TGCGCACCTA TTGGTCCCAG   120
CGGCCCCGCT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA                      162
```

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

```
TCTCACTCCT CGAGGATGGA GGACATCAAG AACTCGGGGT GGAGGGACTC TTGTAGGTGG    60
GGTGACCTGA GGCCTGGTTG TGGTAGCCGC CAGTGGTACC CCTCGAATAT GCGTTCTAGC   120
AGAGATTACC CCGCGGGGGG CCACTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA      177
```

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 152 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

```
TCTCACTCCT CGAGTCATCC GTGGTACAGG CATTGGAACC ATGGTGACTT CTCTGGTTCG    60
GGCCAGTCAC GCCACACCCC GCCGGAGAGC CCCCACCCCG GCCGCCCTAA TGCCACCATT   120
TCTAGAATCG AAGGTCGCGC TAGACCTTCG AG                                 152
```

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

```
TCTCACTCCT CGAGATATAA GCACGATATC GGTTGCGATG CTGGGGTTGA CAAGAAGTCG    60
TCGTCTGTGC GTGGTGGTTG TGGTGCTCAT TNGTCGCCAC CCCGCGCCGG CCGTGGTCCT   120
CGCGGCACGA TGGTTAGCAG GCTTTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA      177
```

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

```
TCTCACTCCT CGAGTCAGGG CTCCAAGCAG TGTATGCAGT ACCGCACCGG TCGTTTGACG     60
GTGGGGTCTG AGTATGGTTG TGGTATGAAC CCCGCCCGCC ATGCCACGCC CGCTTATCCG    120
GCGCGCCTGC TGCCACGCTA TCGCTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA       177
```

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

```
TCTCACTCCT CGAGTGGGCG GACTACTAGT GAGATTTCTG GGCTCTGGGG TTGGGGTGAC     60
GACCGGAGCG GTTATGGTTG GGGTAACACG CTCCGCCCCA ACTACATCCC TTATAGGCAG    120
GCGACGAACA GGCATCGTTA TACGTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA       177
```

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

```
TCTCACTCCT CGAGGTGGAA TTGGACTGTC TTGCCCGCCA CTGGCGGCCA TTACTGGACG     60
CGTTCGACGG ACTATCACGC CATTAACAAT CACAGGCCGA GCATCCCCCA CCAGCATCCG    120
ACCCCTATCT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA                       162
```

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

```
TCTCACTCCT CGAGTTGGTC GTCGTGGAAT TGGAGCTCTA AGACTACTCG TCTGGGCGAC     60
AGGGCGACTC GGGAGGGTTG TGGTCCCAGC CAGTCTGATG GCTGTCCTTA TAACGGCCGC    120
CTTACGACCG TCAAGCCTCG CACGTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA       177
```

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 156 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

```
TCTCACTCCT CGAGTGGTAG TTTGAACGCA TGGCAACCGC GGTCATGGGT GGGGGGCGCG    60
TTCCGGTCAC ACGCCAACAA TAACTTGAAC CCCAAGCCCA CCATGGTTAC TNGTCACCCT   120
ACCTCTAGAA TCGAAGGTCG CGCTAGACCT TCGAGA                             156
```

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 178 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

```
TCTCACTCCT CGAGGTATTC GGGTTTGTCC CCGCGGGACA ACGGTCCCGC TTGTAGTCAG    60
GAGGCTACCT TGGAGGGTTG TGGTGCGCAG AGGCTGATGT CCACCCGTCG CAAGGGCCGC   120
AACTCCCGCC CCGGGTGGAC GCTCTCTAGA ATCGAAGGTC GCGCTAGACC CTTCGAGA     178
```

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

```
TCTCACTCCT CGAGCGTGGG GAATGATAAG ACTAGCAGGC CGGTTTCCTT CTACGGGCGC    60
GTTAGTGATC TGTGGAACGC CAGCTTGATG CCGAAGCGTA CTCCCAGCTC GAAGCGCCAC   120
GATGATGGCT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA                      162
```

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

```
TCTCACTCCT CGAGTACTCC CCCCAGTAGG GAGGCGTATA GTAGGCCCTA TAGTGTCGAT    60
AGCGATTCGG ATACGAACGC CAAGCACAGC TCCCACAACC GCCGTNTGCG GACGCGCAGC   120
CGCCCGAACT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA                      162
```

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 159 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

```
TCTCACTCCT CGAGATGGCC TAGTGTGGGT TACAAGGGTA ATGGCAGTGA CACTATTGAT    60
GTTCACAGCA ATGACGCCAG TACTAAGAGG TCCCTCATCT ATAACCACCG CCGCCCCNTC   120
TTTCCCTCTA GAATCGAAGG TCGCGCTAGA CCTTCGAGA                          159
```

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

```
TCTCACTCCT CGAGAACGTT TGAGAACGAC GGGCTGGGCG TCGGCCGGTC TATTCAGAAG    60
AAGTCGGATA GGTGGTACGC CAGCCACAAC ATTCGTAGCC ATTTCGCGTC CATGTCTCCC   120
GCTGGTAAGT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA                      162
```

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 160 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

```
TCTCACTCCT CGAGCTATTG TCGGGTTAAG GGTGGTGGGG AGGGGGGGCA TACGGATTCC    60
AATCTGGCTA GGTCGGGTTG TGGTAAGGTG GCCAGGACCA GCAGGCTTCA GCATATCAAC   120
CCGCGCGCTA CCCCCCCCTC CCGGTCTAGA ATCGAAGGTC                         160
```

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

```
TCTCACTCCT CGAGTTGGAC TCGGTGGGGC AAGCACANTC ATGGGGGGTT TGTGAACAAG    60
TCTCCCCCTG GGAAGAACGC CACGAGCCCC TACACCGACG CCCAGCTGCC CAGTGATCAG   120
GGTCCTCCCT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA                      162
```

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

```
TCTCACTCCT CGAGTCAGGT TGATTCGTTT CGTAATAGCT TTCGGTGGTA TGAGCCGAGC     60
AGGGCTCTGT GCCATGGTTG TGGTAAGCGC GACACCTCCA CCACTCGTAT CCACAATAGC    120
CCCAGCGACT CCTATCCTAC ACGCTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA       177
```

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

```
TCTCACTCCT CGAGCTTTTT GCGGTTCCAG AGTCCGAGGT TCGAGGATTA CAGTAGGACG     60
ATCTNTCGGT TGCGCAACGC CACGAACCCG AGTAATGTCT CCGATGCGCA CAATAACCGG    120
GCCTTGGCCT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA                       162
```

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

```
TCTCACTCCT CGAGGAGCAT CACCGACGGG GGCATCAATG AGGTGGACCT GAGTAGTGTG     60
TCGAACGTTC TTGAGAACGC CAACTCGCAT AGGGCCTACA GGAAGCATCG CCCGACCTTG    120
AAGCGTCCTT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA                       162
```

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

```
TCTCACTCCT CGAGTTCGAA GGTGAGCAGC CCGAGGGATC CGACGGTCCC GCGGAAGGGC     60
GGCAATGTTG ATTATGGTTG TGGTCACAGG TCTTCCGCCC GGATGCCTAC CTCCGCTCTG    120
TCGTCGATCA CGAAGTGCTA CACTTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA       177
```

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

```
TCTCACTCCT CGAGAGCCAG TANGCAGGGC GGCCGGGGTG TTGCCCCTGA GTTTGGGGCG    60
AGCGTTTTGG GTNGTGGTTG TGGTAGCGCC ACTTATTACA CGAACTCCAC CAGCTGCAAG   120
GATGCTATGG GCCACAACTA CTCGTCTAGA ATCGAAGGTC GCGNTAGACC TTCGAGA      177
```

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

```
TCTCACTCCT CGAGATGGTG CGAGAAGCAC AAGTTTACGG CTGCGCGTTG CAGCGCGGGG    60
GCGGGTTTTG AGAGGGANGC CAGCCGTCCG CCCCAGCCTG CCCACCGGGA TAATACCAAC   120
CGTAATGCNT NTAGAATCGA AGGTCGCGCT AGACCTTCGA GA                      162
```

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

```
TCTCACTCCT CGAGTTTTCA GGTGTACCCG GACCATGGTC TGGAGAGGCA TGCTTTGGAC    60
GGGACGGGTC CGCTTTACGC CATGCCCGGC CGCTGGATTA GGGCGCGTCC GCAGAACAGG   120
GACCGCCAGT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA                      162
```

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 159 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

```
TCTCACTCCT CGAGCAGGTG TACGGACAAC GAGCAGTGCC CCGATACCGG GANTAGGTCT    60
CGTTCCGTTA GTAACGCCAG GTACTTTTCG AGCAGGTTGC TCAAGACTCA CGCCCCCCAT   120
CGCCCTTCTA GAATCGAAGG TCGCGCTAGA CCTTCGAGA                          159
```

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

TCTCACTCCT CGAGTGCCAG GGATAGCGGG CCTGCGGAGG ATGGGTCCCG CGCCGTCCGG 60
TTGAACGGGG TTGAGAACGC CAACACTAGG AAGTCCTCCC GCAGTAACCC GCGGGGTAGG 120
CGCCATCCCT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA 162

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

TCTCACTCCT CGAGTTCCGC CGATGCGGAG AAGTGTGCGG GCAGTCTGTT GTGGTGGGGT 60
AGGCAGAACA ACTCCGGTTG TGGTTCGCCC ACGAAGAAGC ATCTGAAGCA CCGCAATCGC 120
AGTCAGACCT CCTCTTCGTC CCACTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA 177

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

TCTCACTCCT CGAGACCGAA GAACGTGGCC GATGCTTATT CGTCTCAGGA CGGGGCGGCG 60
GCCGAGGAGA CGTCTCACGC CAGTAATGCC GCGCGGAAGT CCCCTAAGCA CAAGCCCTTG 120
AGGCGGCCTT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA 162

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

TCTCACTCCT CGAGAGGCAG TACGGGGACG GCCGGCGGCG AGCGTTCCGG GGTGCTCAAC 60
CTGCACACCA GGGATAACGC CAGCGGCAGC GGTTTCAAAC CGTGGTACCC TTCGAATCGG 120
GGTCACAAGT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA 162

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

TCTCACTCCT CGAGGTGGGG GTGGGAGAGG AGTCCGTCCG ACTACGATTC TGATATGGAC 60
TTGGGGGCGA GGAGGTACGC CACCCGCACC CACCGCGCGC CCCCTCGCGT CTTGAAGGCT 120

CCCCTGCCCT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA 162

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

```
TCTCACTCCT CGAGGCACTG GAAGTGCGAG GGCTCTCAGG CTGCCTACGG GGACAAGGAT     60
ATCGGGAGGT CCAGGGGTTG TGGTTCCATT ACAAAGAATA ACACTAATCA CGCCCATCCT    120
AGCCACGGCG CCGTTGCTAA GATCTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA       177
```

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

```
TCTCACTCCT CGAGCCGCGA GGAGGCGAAC TGGGACGGCT ATAAGAGGGA GATGAGCCAC     60
CGGAGTCGCT TTTGGGACGC CACCCACCTG TCCCGCCCTC GCCGCCCCGC TAACTCTGGT    120
GACCCTAACT CTAGAATCGA AGGTCGCGCT AGACCTTCGA GA                       162
```

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

```
TCTCACTCNT CGAGAGAGTT CGCGGAGAGG AGGTTGTGGG GGTGTGATGA CCTGAGTTGG     60
CGTCTCGACG CGGAGGGTTG TGGTCCCACT CCGAGCAATC GGGCCGTCAA GCATCGCAAG    120
CCCCGCCCAC GCTCCCCCGC ACTCTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA       177
```

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

```
TCTCACTCNT NGAGTGATCA CGCGTTGGGG ACGAATCTGA GGTCTGACAA TGCCAAGGAG     60
CCGGGTGATT ACAACTGTTG TGGTAACGGG AACTCTACCG GGCGAAAGGT TTTTAACCGT    120
AGGCGCCCCT CCGCCATCCC CANTTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA       177
```

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

TCTCACTCCT CGAGGCATAT TTCTGAGTAT AGCTTTGCGA ATTCCCACTT GATGGGTGGC 60
GAGTCCAAGC GGAAGGGTTG TGGTATTAAC GGCTCCTTTT CTCCCACTTG TCCCCGCTCC 120
CCCACCCCAG CCTTCCGCCG CACCTCTAGA ATCGAAGGTC GCGCTAGACC TTCGAGA 177

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 158 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

TCTCACTCCT CGAGCCGGGA GAGCGGGATG TGGGGTAGTT GGTGGCGTGG TCACAGGTTG 60
AATTCCACGG GGGGTAACGC CAACATGAAT GCTAGTCTGC CCCCCGACCC CCCTGTTTCC 120
ACTCCGTCTA GAATCGAAGG TCGCGCTAGA CCTTCGAG 158

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 708 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

Met Gly Met Ser Lys Ser His Ser Phe Phe Gly Tyr Pro Leu Ser Ile
1 5 10 15
Phe Phe Ile Val Val Asn Glu Phe Cys Glu Arg Phe Ser Tyr Tyr Gly
20 25 30
Met Arg Ala Ile Leu Ile Leu Tyr Phe Thr Asn Phe Ile Ser Trp Asp
35 40 45
Asp Asn Leu Ser Thr Ala Ile Tyr His Thr Phe Val Ala Leu Cys Tyr
50 55 60
Leu Thr Pro Ile Leu Gly Ala Leu Ile Ala Asp Ser Trp Leu Gly Lys
65 70 75 80
Phe Lys Thr Ile Val Ser Leu Ser Ile Val Tyr Thr Ile Gly Gln Ala
85 90 95
Val Thr Ser Val Ser Ser Ile Asn Asp Leu Thr Asp His Asn His Asp
100 105 110
Gly Thr Pro Asp Ser Leu Pro Val His Val Val Leu Ser Leu Ile Gly
115 120 125
Leu Ala Leu Ile Ala Leu Gly Thr Gly Gly Ile Lys Pro Cys Val Ser
130 135 140
Ala Phe Gly Gly Asp Gln Phe Glu Glu Gly Gln Glu Lys Gln Arg Asn
145 150 155 160
Arg Phe Phe Ser Ile Phe Tyr Leu Ala Ile Asn Ala Gly Ser Leu Leu
165 170 175

Ser Thr Ile Ile Thr Pro Met Leu Arg Val Gln Gln Cys Gly Ile His
180 185 190
Ser Lys Gln Ala Cys Tyr Pro Leu Ala Phe Gly Val Pro Ala Ala Leu
195 200 205
Met Ala Val Ala Leu Ile Val Phe Val Leu Gly Ser Gly Met Tyr Lys
210 215 220
Lys Phe Lys Pro Gln Gly Asn Ile Met Gly Lys Val Ala Lys Cys Ile
225 230 235 240
Gly Phe Ala Ile Lys Asn Arg Phe Arg His Arg Ser Lys Ala Phe Pro
245 250 255
Lys Arg Glu His Trp Leu Asp Trp Ala Lys Glu Lys Tyr Asp Glu Arg
260 265 270
Leu Ile Ser Gln Ile Lys Met Val Thr Arg Val Met Phe Leu Tyr Ile
275 280 285
Pro Leu Pro Met Phe Trp Ala Leu Phe Asp Gln Gln Gly Ser Arg Trp
290 295 300
Thr Leu Gln Ala Thr Thr Met Ser Gly Lys Ile Gly Ala Leu Glu Ile
305 310 315 320
Gln Pro Asp Gln Met Gln Thr Val Asn Ala Ile Leu Ile Val Ile Met
325 330 335
Val Pro Ile Phe Asp Ala Val Leu Tyr Pro Leu Ile Ala Lys Cys Gly
340 345 350
Phe Asn Phe Thr Ser Leu Lys Lys Met Ala Val Gly Met Val Leu Ala
355 360 365
Ser Met Ala Phe Val Val Ala Ala Ile Val Gln Val Glu Ile Asp Lys
370 375 380
Thr Leu Pro Val Phe Pro Lys Gly Asn Glu Val Gln Ile Lys Val Leu
385 390 395 400
Asn Ile Gly Asn Asn Thr Met Asn Ile Ser Leu Pro Gly Glu Met Val
405 410 415
Thr Leu Gly Pro Met Ser Gln Thr Asn Ala Phe Met Thr Phe Asp Val
420 425 430
Asn Lys Leu Thr Arg Ile Asn Ile Ser Ser Pro Gly Ser Pro Val Thr
435 440 445
Ala Val Thr Asp Asp Phe Lys Gln Gly Gln Arg His Thr Leu Leu Val
450 455 460
Trp Ala Pro Asn His Tyr Gln Val Val Lys Asp Gly Leu Asn Gln Lys
465 470 475 480
Pro Glu Lys Gly Glu Asn Gly Ile Arg Phe Val Asn Thr Phe Asn Glu
485 490 495
Leu Ile Thr Ile Thr Met Ser Gly Lys Val Tyr Ala Asn Ile Ser Ser
500 505 510
Tyr Asn Ala Ser Thr Tyr Gln Phe Phe Pro Ser Gly Ile Lys Gly Phe
515 520 525
Thr Ile Ser Ser Thr Glu Ile Pro Pro Gln Cys Gln Pro Asn Phe Asn
530 535 540
Thr Phe Tyr Leu Glu Phe Gly Ser Ala Tyr Thr Tyr Ile Val Gln Arg
545 550 555 560
Lys Asn Asp Ser Cys Pro Glu Val Lys Val Phe Glu Asp Ile Ser Ala
565 570 575
Asn Thr Val Asn Met Ala Leu Gln Ile Pro Gln Tyr Phe Leu Leu Thr
580 585 590
Cys Gly Glu Val Val Phe Ser Val Thr Gly Leu Glu Phe Ser Tyr Ser
595 600 605
Gln Ala Pro Ser Asn Met Lys Ser Val Leu Gln Ala Gly Trp Leu Leu
610 615 620
Thr Val Ala Val Gly Asn Ile Ile Val Leu Ile Val Ala Gly Ala Gly
625 630 635 640
Gln Phe Ser Lys Gln Trp Ala Glu Tyr Ile Leu Phe Ala Ala Leu Leu
645 650 655
Leu Val Val Cys Val Val Phe Ala Ile Met Ala Arg Phe Tyr Thr Tyr
660 665 670
Ile Asn Pro Ala Glu Ile Glu Ala Gln Phe Asp Glu Asp Glu Lys Lys
675 680 685
Asn Arg Leu Glu Lys Ser Asn Pro Tyr Phe Met Ser Gly Ala Asn Ser
690 695 700

Gln Lys Gln Met
705

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

TCCGGACTCT CATAAGCGCC GG 22

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

ACAACGGGCC AGAAAGAGCG AG 22

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

ACACCACCCC AATCGGAGCT AC 22

(2) INFORMATION FOR SEQ ID NO:114:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

TCAGAATCCG TGCACTGGCC AA 22

(2) INFORMATION FOR SEQ ID NO:115:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

GCCCTATTCA TACCACCGGA GT 22

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

CATCAGTCCT ACCGCCGAAA AG 22

(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

CGTATAGCTA TTGTGAGCGA TG 22

(2) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

ACGCGCGGAA CGAGCAGTAC CA 22

(2) INFORMATION FOR SEQ ID NO:119:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

CCATAATGAT CCCCGTCACT AT 22

(2) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

AGACACCCCT TAGCCGTCGT AG 22

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

AGCTCCGTGA CCTTAGTCAT AA 22

(2) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

TGCACAGCTC AGCGCCGCAC CA 22

(2) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

ACGGGTCATC AGCGCCGCAC CA 22

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

TGTCACCCCC CTCCCCGGAC TT 22

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

ACTCGCAATT ATTGGCGCTC GA 22

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

GTCTTCTCAA CCTTATCCTG CG 22

(2) INFORMATION FOR SEQ ID NO:127:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

AAAGCCCCCT GCTAAACTCC CA 22

(2) INFORMATION FOR SEQ ID NO:128:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

CTGCGTCTGC CACGTCGTCA TC 22

(2) INFORMATION FOR SEQ ID NO:129:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

GTTAAAAGAG GGCAAGCTCG GA 22

(2) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

CCGAGTTCTT GATGTCCTCC AT 22

(2) INFORMATION FOR SEQ ID NO:131:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

TCCAATGCCT GTACCACGGA TG 22

(2) INFORMATION FOR SEQ ID NO:132:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

TCGCAACCGA TATCGTGCTT AT 22

(2) INFORMATION FOR SEQ ID NO:133:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

TGCATACACT GCTTGGAGCC CT 22

(2) INFORMATION FOR SEQ ID NO:134:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

GAAATCTCAC TAGTAGTCCG CC 22

(2) INFORMATION FOR SEQ ID NO:135:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

GCGGGCAAGA CAGTCCAATT CC 22

(2) INFORMATION FOR SEQ ID NO:136:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:

GAGCTCCAAT TCCACGACGA CC 22

(2) INFORMATION FOR SEQ ID NO:137:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

GGTTGCCATG CGTTCAAACT AC 22

(2) INFORMATION FOR SEQ ID NO:138:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:138:

TCCCGCGGGG ACAAACCCGA AT 22

(2) INFORMATION FOR SEQ ID NO:139:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

CTGCTAGTCT TATCATTCCC CA 22

(2) INFORMATION FOR SEQ ID NO:140:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

CTATCGACAC TATAGGGCCT AC 22

(2) INFORMATION FOR SEQ ID NO:141:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:141:

TACCCTTGTA ACCCACACTA GG 22

(2) INFORMATION FOR SEQ ID NO:142:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:

TTCTTCTGAA TAGACCGGCC GA 22

(2) INFORMATION FOR SEQ ID NO:143:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:143:

CCACCACCCT TAACCCGACA AT 22

(2) INFORMATION FOR SEQ ID NO:144:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:144:

AGGGGGAGAC TTGTTCACAA AC 22

(2) INFORMATION FOR SEQ ID NO:145:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:145:

CGGCTCATAC CACCGAAAGC TA 22

(2) INFORMATION FOR SEQ ID NO:146:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:146:

ATCGTCCTAC TGTAATCCTC GA 22

(2) INFORMATION FOR SEQ ID NO:147:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:147:

GACACACTAC TCAGGTCCAC CT 22

(2) INFORMATION FOR SEQ ID NO:148:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:148:

CCATAATCAA CATTGCCGCC CT 22

(2) INFORMATION FOR SEQ ID NO:149:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:149:

CAAAACGCTC GCCCCAAACT CA 22

(2) INFORMATION FOR SEQ ID NO:150:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:150:

GTAAACTTGT GCTTCTCGCA CC 22

(2) INFORMATION FOR SEQ ID NO:151:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:151:

CCATGGTCCG GGTACACCTG AA 22

(2) INFORMATION FOR SEQ ID NO:152:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:152:

GTTACTAACG GAACGAGACC TA 22

(2) INFORMATION FOR SEQ ID NO:153:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:153:

TGTTGGCGTT CTCAACCCCG TT 22

(2) INFORMATION FOR SEQ ID NO:154:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:154:

ACAACCGGAG TTGTTCTGCC TA 22

(2) INFORMATION FOR SEQ ID NO:155:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:155:

TAAGCATCGG CCACGTTCTT CG 22

(2) INFORMATION FOR SEQ ID NO:156:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:156:

TTATCCCTGG TGTGCAGGTT GA 22

(2) INFORMATION FOR SEQ ID NO:157:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:157:

TATCAGAATC GTAGTCGGAC GG 22

(2) INFORMATION FOR SEQ ID NO:158:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:158:

CTTTGTAATG GAACCACAAC CC 22

(2) INFORMATION FOR SEQ ID NO:159:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:159:

CGGTGGCTCA TCTCCCTCTT AT 22

(2) INFORMATION FOR SEQ ID NO:160:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:160:

ATCAGACTGG CTGGGACCAC AA 22

(2) INFORMATION FOR SEQ ID NO:161:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:161:

CACAACCTCC TCTCCGCGAA CT 22

(2) INFORMATION FOR SEQ ID NO:162:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:162:

AGATTCGTCC CCAACGCGTG AT 22

(2) INFORMATION FOR SEQ ID NO:163:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:163:

GGGAATTCGC AAAGCTATAC TC 22

(2) INFORMATION FOR SEQ ID NO:164:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:164:

CCCCGTGGAA TTCAACCTGT GA 22

(2) INFORMATION FOR SEQ ID NO:165:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:165:

GTCGTCTTTC CAGACGT 17

(2) INFORMATION FOR SEQ ID NO:166:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:166:

CTTGCATGCC TGCAGGTCGA C 21

(2) INFORMATION FOR SEQ ID NO:167:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:167:

```
Arg Ile Ala Gly Leu Pro Trp Tyr Arg Cys Arg Thr Val Ala Phe Glu
 1               5                  10                  15
Thr Gly Met Gln Asn Thr Gln Leu Cys Ser Thr Ile Val Gln Leu Ser
            20                  25                  30
Phe Thr Pro Glu Glu
        35
```

(2) INFORMATION FOR SEQ ID NO:168:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:168:

```
Arg Glu Phe Ala Glu Arg Arg Leu Trp Gly Cys Asp Asp Leu Ser Trp
 1               5                  10                  15
Arg Leu Asp Ala Glu Gly Cys Gly Pro Thr Pro Ser Asn Arg Ala Val
            20                  25                  30
Lys His Arg Lys Pro Arg Pro Arg Ser Pro Ala Leu
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:169:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 41 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:169:

```
Ser Gly Ser His Ser Gly Gly Met Asn Arg Ala Tyr Gly Asp Val Phe
 1               5                  10                  15
Arg Glu Leu Arg Asp Arg Trp Tyr Ala Thr Ser His His Thr Arg Pro
            20                  25                  30
Thr Pro Gln Leu Pro Arg Gly Pro Asn
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:170:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:170:

```
Ser Thr Pro Pro Ser Arg Glu Ala Tyr Ser Arg Pro Tyr Ser Val Asp
 1               5                  10                  15
Ser Asp Ser Asp
            20
```

(2) INFORMATION FOR SEQ ID NO:171:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:171:

```
Ser Thr Pro Pro Ser Arg Glu Ala Tyr Ser Arg Pro Tyr Ser Val Asp
 1               5                  10                  15
Ser Asp Ser Asp Thr Asn Ala Lys His Ser Ser His Asn
            20                  25
```

(2) INFORMATION FOR SEQ ID NO:172:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:172:

```
Thr Asn Ala Lys His Ser Ser His Asn Arg Arg Leu Arg Thr Arg Ser
 1               5                  10                  15
Arg Pro Asn
```

(2) INFORMATION FOR SEQ ID NO:173:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:173:

```
Thr Asn Ala Lys His Ser Ser His Asn
 1               5
```

(2) INFORMATION FOR SEQ ID NO:174:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:174:

```
Ser Ser His Asn Arg Arg Leu Arg Thr Arg Ser Arg Pro Asn
 1               5                  10
```

(2) INFORMATION FOR SEQ ID NO:175:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:175:

Arg Arg Leu Arg Thr Arg Ser Arg Pro Asn
1 5 10

(2) INFORMATION FOR SEQ ID NO:176:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 708 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:176:

Met Gly Met Ser Lys Ser His Ser Phe Phe Gly Tyr Pro Leu Ser Ile
1 5 10 15
Phe Phe Ile Val Val Asn Glu Phe Cys Glu Arg Phe Ser Tyr Tyr Gly
20 25 30
Met Arg Ala Ile Leu Ile Leu Tyr Phe Thr Asn Phe Ile Ser Trp Asp
35 40 45
Asp Asn Leu Ser Thr Ala Ile Tyr His Thr Phe Val Ala Leu Cys Tyr
50 55 60
Leu Thr Pro Ile Leu Gly Ala Leu Ile Ala Asp Ser Trp Leu Gly Lys
65 70 75 80
Phe Lys Thr Ile Val Ser Leu Ser Ile Val Tyr Thr Ile Gly Gln Ala
85 90 95
Val Thr Ser Val Ser Ser Ile Asn Asp Leu Thr Asp His Asn His Asp
100 105 110
Gly Thr Pro Asp Ser Leu Pro Val His Val Val Leu Ser Leu Ile Gly
115 120 125
Leu Ala Leu Ile Ala Leu Gly Thr Gly Gly Ile Lys Pro Cys Val Ser
130 135 140
Ala Phe Gly Gly Asp Gln Phe Glu Glu Gly Gln Glu Lys Gln Arg Asn
145 150 155 160
Arg Phe Phe Ser Ile Phe Tyr Leu Ala Ile Asn Ala Gly Ser Leu Leu
165 170 175
Ser Thr Ile Ile Thr Pro Met Leu Arg Val Gln Gln Cys Gly Ile His
180 185 190
Ser Lys Gln Ala Cys Tyr Pro Leu Ala Phe Gly Val Pro Ala Ala Leu
195 200 205
Met Ala Val Ala Leu Ile Val Phe Val Leu Gly Ser Gly Met Tyr Lys
210 215 220
Lys Phe Lys Pro Gln Gly Asn Ile Met Gly Lys Val Ala Lys Cys Ile
225 230 235 240
Gly Phe Ala Ile Lys Asn Arg Phe Arg His Arg Ser Lys Ala Phe Pro
245 250 255
Lys Arg Glu His Trp Leu Asp Trp Ala Lys Glu Lys Tyr Asp Glu Arg
260 265 270
Leu Ile Ser Gln Ile Lys Met Val Thr Arg Val Met Phe Leu Tyr Ile
275 280 285
Pro Leu Pro Met Phe Trp Ala Leu Phe Asp Gln Gln Gly Ser Arg Trp
290 295 300
Thr Leu Gln Ala Thr Thr Met Ser Gly Lys Ile Gly Ala Leu Glu Ile
305 310 315 320
Gln Pro Asp Gln Met Gln Thr Val Asn Ala Ile Leu Ile Val Ile Met

```
                        325                          330                          335
Val Pro Ile Phe Asp Ala Val Leu Tyr Pro Leu Ile Ala Lys Cys Gly
                340                          345                          350
Phe Asn Phe Thr Ser Leu Lys Lys Met Ala Val Gly Met Val Leu Ala
            355                          360                          365
Ser Met Ala Phe Val Val Ala Ala Ile Val Gln Val Glu Ile Asp Lys
    370                          375                          380
Thr Leu Pro Val Phe Pro Lys Gly Asn Glu Val Gln Ile Lys Val Leu
385                          390                          395                          400
Asn Ile Gly Asn Asn Thr Met Asn Ile Ser Leu Pro Gly Glu Met Val
                        405                          410                          415
Thr Leu Gly Pro Met Ser Gln Thr Asn Ala Phe Met Thr Phe Asp Val
                420                          425                          430
Asn Lys Leu Thr Arg Ile Asn Ile Ser Ser Pro Gly Ser Pro Val Thr
            435                          440                          445
Ala Val Thr Asp Asp Phe Lys Gln Gly Gln Arg His Thr Leu Leu Val
    450                          455                          460
Trp Ala Pro Asn His Tyr Gln Val Val Lys Asp Gly Leu Asn Gln Lys
465                          470                          475                          480
Pro Glu Lys Gly Glu Asn Gly Ile Arg Phe Val Asn Thr Phe Asn Glu
                        485                          490                          495
Leu Ile Thr Ile Thr Met Ser Gly Lys Val Tyr Ala Asn Ile Ser Ser
                500                          505                          510
Tyr Asn Ala Ser Thr Tyr Gln Phe Phe Pro Ser Gly Ile Lys Gly Phe
            515                          520                          525
Thr Ile Ser Ser Thr Glu Ile Pro Pro Gln Cys Gln Pro Asn Phe Asn
    530                          535                          540
Thr Phe Tyr Leu Glu Phe Gly Ser Ala Tyr Thr Tyr Ile Val Gln Arg
545                          550                          555                          560
Lys Asn Asp Ser Cys Pro Glu Val Lys Val Phe Glu Asp Ile Ser Ala
                        565                          570                          575
Asn Thr Val Asn Met Ala Leu Gln Ile Pro Gln Tyr Phe Leu Leu Thr
                580                          585                          590
Cys Gly Glu Val Val Phe Ser Val Thr Gly Leu Glu Phe Ser Tyr Ser
            595                          600                          605
Gln Ala Pro Ser Asn Met Lys Ser Val Leu Gln Ala Gly Trp Leu Leu
    610                          615                          620
Thr Val Ala Val Gly Asn Ile Ile Val Leu Ile Val Ala Gly Ala Gly
625                          630                          635                          640
Gln Phe Ser Lys Gln Trp Ala Glu Tyr Ile Leu Phe Ala Ala Leu Leu
                        645                          650                          655
Leu Val Val Cys Val Val Phe Ala Ile Met Ala Arg Phe Tyr Thr Tyr
                660                          665                          670
Ile Asn Pro Ala Glu Ile Glu Ala Gln Phe Asp Glu Asp Glu Lys Lys
            675                          680                          685
Asn Arg Leu Glu Lys Ser Asn Pro Tyr Phe Met Ser Gly Ala Asn Ser
    690                          695                          700
Gln Lys Gln Met
705
```

(2) INFORMATION FOR SEQ ID NO:177:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3345 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 88...2583
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:177:

```
GAATTCCGTC TCGACCACTG AATGGAAGAA AAGGACTTTT AACCACCATT TTGTGACTTA      60
CAGAAAGGAA TTTGAATAAA GAAAACT ATG ATA CTT CAG GCC CAT CTT CAC TCC     114
                              Met Ile Leu Gln Ala His Leu His Ser
                               1               5

CTG TGT CTT CTT ATG CTT TAT TTG GCA ACT GGA TAT GGC CAA GAG GGG       162
Leu Cys Leu Leu Met Leu Tyr Leu Ala Thr Gly Tyr Gly Gln Glu Gly
10                  15                  20                  25

AAG TTT AGT GGA CCC CTG AAA CCC ATG ACA TTT TCT ATT TAT GAA GGC       210
Lys Phe Ser Gly Pro Leu Lys Pro Met Thr Phe Ser Ile Tyr Glu Gly
                30                  35                  40

CAA GAA CCG AGT CAA ATT ATA TTC CAG TTT AAG GCC AAT CCT CCT GCT       258
Gln Glu Pro Ser Gln Ile Ile Phe Gln Phe Lys Ala Asn Pro Pro Ala
            45                  50                  55

GTG ACT TTT GAA CTA ACT GGG GAG ACA GAC AAC ATA TTT GTG ATA GAA       306
Val Thr Phe Glu Leu Thr Gly Glu Thr Asp Asn Ile Phe Val Ile Glu
        60                  65                  70

CGG GAG GGA CTT CTG TAT TAC AAC AGA GCC TTG GAC AGG GAA ACA AGA       354
Arg Glu Gly Leu Leu Tyr Tyr Asn Arg Ala Leu Asp Arg Glu Thr Arg
    75                  80                  85

TCT ACT CAC AAT CTC CAG GTT GCA GCC CTG GAC GCT AAT GGA ATT ATA       402
Ser Thr His Asn Leu Gln Val Ala Ala Leu Asp Ala Asn Gly Ile Ile
90                  95                  100                 105

GTG GAG GGT CCA GTC CCT ATC ACC ATA GAA GTG AAG GAC ATC AAC GAC       450
Val Glu Gly Pro Val Pro Ile Thr Ile Glu Val Lys Asp Ile Asn Asp
                110                 115                 120

AAT CGA CCC ACG TTT CTC CAG TCA AAG TAC GAA GGC TCA GTA AGG CAG       498
Asn Arg Pro Thr Phe Leu Gln Ser Lys Tyr Glu Gly Ser Val Arg Gln
            125                 130                 135

AAC TCT CGC CCA GGA AAG CCC TTC TTG TAT GTC AAT GCC ACA GAC CTG       546
Asn Ser Arg Pro Gly Lys Pro Phe Leu Tyr Val Asn Ala Thr Asp Leu
        140                 145                 150

GAT GAT CCG GCC ACT CCC AAT GGC CAG CTT TAT TAC CAG ATT GTC ATC       594
Asp Asp Pro Ala Thr Pro Asn Gly Gln Leu Tyr Tyr Gln Ile Val Ile
    155                 160                 165

CAG CTT CCC ATG ATC AAC AAT GTC ATG TAC TTT CAG ATC AAC AAC AAA       642
Gln Leu Pro Met Ile Asn Asn Val Met Tyr Phe Gln Ile Asn Asn Lys
170                 175                 180                 185

ACG GGA GCC ATC TCT CTT ACC CGA GAG GGA TCT CAG GAA TTG AAT CCT       690
Thr Gly Ala Ile Ser Leu Thr Arg Glu Gly Ser Gln Glu Leu Asn Pro
                190                 195                 200

GCT AAG AAT CCT TCC TAT AAT CTG GTG ATC TCA GTG AAG GAC ATG GGA       738
Ala Lys Asn Pro Ser Tyr Asn Leu Val Ile Ser Val Lys Asp Met Gly
            205                 210                 215

GGC CAG AGT GAG AAT TCC TTC AGT GAT ACC ACA TCT GTG GAT ATC ATA       786
Gly Gln Ser Glu Asn Ser Phe Ser Asp Thr Thr Ser Val Asp Ile Ile
        220                 225                 230

GTG ACA GAG AAT ATT TGG AAA GCA CCA AAA CCT GTG GAG ATG GTG GAA       834
Val Thr Glu Asn Ile Trp Lys Ala Pro Lys Pro Val Glu Met Val Glu
    235                 240                 245
```

```
AAC TCA ACT GAT CCT CAC CCC ATC AAA ATC ACT CAG GTG CGG TGG AAT      882
Asn Ser Thr Asp Pro His Pro Ile Lys Ile Thr Gln Val Arg Trp Asn
250                 255                 260                 265

GAT CCC GGT GCA CAA TAT TCC TTA GTT GAC AAA GAG AAG CTG CCA AGA      930
Asp Pro Gly Ala Gln Tyr Ser Leu Val Asp Lys Glu Lys Leu Pro Arg
            270                 275                 280

TTC CCA TTT TCA ATT GAC CAG GAA GGA GAT ATT TAC GTG ACT CAG CCC      978
Phe Pro Phe Ser Ile Asp Gln Glu Gly Asp Ile Tyr Val Thr Gln Pro
        285                 290                 295

TTG GAC CGA GAA GAA AAG GAT GCA TAT GTT TTT TAT GCA GTT GCA AAG     1026
Leu Asp Arg Glu Glu Lys Asp Ala Tyr Val Phe Tyr Ala Val Ala Lys
    300                 305                 310

GAT GAG TAC GGA AAA CCA CTT TCA TAT CCG CTG GAA ATT CAT GTA AAA     1074
Asp Glu Tyr Gly Lys Pro Leu Ser Tyr Pro Leu Glu Ile His Val Lys
    315                 320                 325

GTT AAA GAT ATT AAT GAT AAT CCA CCT ACA TGT CCG TCA CCA GTA ACC     1122
Val Lys Asp Ile Asn Asp Asn Pro Pro Thr Cys Pro Ser Pro Val Thr
330                 335                 340                 345

GTA TTT GAG GTC CAG GAG AAT GAA CGA CTG GGT AAC AGT ATC GGG ACC     1170
Val Phe Glu Val Gln Glu Asn Glu Arg Leu Gly Asn Ser Ile Gly Thr
                350                 355                 360

CTT ACT GCA CAT GAC AGG GAT GAA GAA AAT ACT GCC AAC AGT TTT CTA     1218
Leu Thr Ala His Asp Arg Asp Glu Glu Asn Thr Ala Asn Ser Phe Leu
        365                 370                 375

AAC TAC AGG ATT GTG GAG CAA ACT CCC AAA CTT CCC ATG GAT GGA CTC     1266
Asn Tyr Arg Ile Val Glu Gln Thr Pro Lys Leu Pro Met Asp Gly Leu
    380                 385                 390

TTC CTA ATC CAA ACC TAT GCT GGA ATG TTA CAG TTA GCT AAA CAG TCC     1314
Phe Leu Ile Gln Thr Tyr Ala Gly Met Leu Gln Leu Ala Lys Gln Ser
    395                 400                 405

TTG AAG AAG CAA GAT ACT CCT CAG TAC AAC TTA ACG ATA GAG GTG TCT     1362
Leu Lys Lys Gln Asp Thr Pro Gln Tyr Asn Leu Thr Ile Glu Val Ser
410                 415                 420                 425

GAC AAA GAT TTC AAG ACC CTT TGT TTT GTG CAA ATC AAC GTT ATT GAT     1410
Asp Lys Asp Phe Lys Thr Leu Cys Phe Val Gln Ile Asn Val Ile Asp
                430                 435                 440

ATC AAT GAT CAG ATC CCC ATC TTT GAA AAA TCA GAT TAT GGA AAC CTG     1458
Ile Asn Asp Gln Ile Pro Ile Phe Glu Lys Ser Asp Tyr Gly Asn Leu
            445                 450                 455

ACT CTT GCT GAA GAC ACA AAC ATT GGG TCC ACC ATC TTA ACC ATC CAG     1506
Thr Leu Ala Glu Asp Thr Asn Ile Gly Ser Thr Ile Leu Thr Ile Gln
        460                 465                 470

GCC ACT GAT GCT GAT GAG CCA TTT ACT GGG AGT TCT AAA ATT CTG TAT     1554
Ala Thr Asp Ala Asp Glu Pro Phe Thr Gly Ser Ser Lys Ile Leu Tyr
    475                 480                 485

CAT ATC ATA AAG GGA GAC AGT GAG GGA CGC CTG GGG GTT GAC ACA GAT     1602
His Ile Ile Lys Gly Asp Ser Glu Gly Arg Leu Gly Val Asp Thr Asp
490                 495                 500                 505

CCC CAT ACC AAC ACC GGA TAT GTC ATA ATT AAA AAG CCT CTT GAT TTT     1650
Pro His Thr Asn Thr Gly Tyr Val Ile Ile Lys Lys Pro Leu Asp Phe
```

```
                    510                     515                     520

GAA ACA GCA GCT GTT TCC AAC ATT GTG TTC AAA GCA GAA AAT CCT GAG     1698
Glu Thr Ala Ala Val Ser Asn Ile Val Phe Lys Ala Glu Asn Pro Glu
                525                     530                     535

CCT CTA GTG TTT GGT GTG AAG TAC AAT GCA AGT TCT TTT GCC AAG TTC     1746
Pro Leu Val Phe Gly Val Lys Tyr Asn Ala Ser Ser Phe Ala Lys Phe
            540                     545                     550

ACG CTT ATT GTG ACA GAT GTG AAT GAA GCA CCT CAA TTT TCC CAA CAC     1794
Thr Leu Ile Val Thr Asp Val Asn Glu Ala Pro Gln Phe Ser Gln His
        555                     560                     565

GTA TTC CAA GCG AAA GTC AGT GAG GAT GTA GCT ATA GGC ACT AAA GTG     1842
Val Phe Gln Ala Lys Val Ser Glu Asp Val Ala Ile Gly Thr Lys Val
570                     575                     580                     585

GGC AAT GTG ACT GCC AAG GAT CCA GAA GGT CTG GAC ATA AGC TAT TCA     1890
Gly Asn Val Thr Ala Lys Asp Pro Glu Gly Leu Asp Ile Ser Tyr Ser
                    590                     595                     600

CTG AGG GGA GAC ACA AGA GGT TGG CTT AAA ATT GAC CAC GTG ACT GGT     1938
Leu Arg Gly Asp Thr Arg Gly Trp Leu Lys Ile Asp His Val Thr Gly
                605                     610                     615

GAG ATC TTT AGT GTG GCT CCA TTG GAC AGA GAA GCC GGA AGT CCA TAT     1986
Glu Ile Phe Ser Val Ala Pro Leu Asp Arg Glu Ala Gly Ser Pro Tyr
            620                     625                     630

CGG GTA CAA GTG GTG GCC ACA GAA GTA GGG GGG TCT TCC TTA AGC TCT     2034
Arg Val Gln Val Val Ala Thr Glu Val Gly Gly Ser Ser Leu Ser Ser
        635                     640                     645

GTG TCA GAG TTC CAC CTG ATC CTT ATG GAT GTG AAT GAC AAC CCT CCC     2082
Val Ser Glu Phe His Leu Ile Leu Met Asp Val Asn Asp Asn Pro Pro
650                     655                     660                     665

AGG CTA GCC AAG GAC TAC ACG GGC TTG TTC TTC TGC CAT CCC CTC AGT     2130
Arg Leu Ala Lys Asp Tyr Thr Gly Leu Phe Phe Cys His Pro Leu Ser
                    670                     675                     680

GCA CCT GGA AGT CTC ATT TTC GAG GCT ACT GAT GAT GAT CAG CAC TTA     2178
Ala Pro Gly Ser Leu Ile Phe Glu Ala Thr Asp Asp Asp Gln His Leu
                685                     690                     695

TTT CGG GGT CCC CAT TTT ACA TTT TCC CTC GGC AGT GGA AGC TTA CAA     2226
Phe Arg Gly Pro His Phe Thr Phe Ser Leu Gly Ser Gly Ser Leu Gln
            700                     705                     710

AAC GAC TGG GAA GTT TCC AAA ATC AAT GGT ACT CAT GCC CGA CTG TCT     2274
Asn Asp Trp Glu Val Ser Lys Ile Asn Gly Thr His Ala Arg Leu Ser
        715                     720                     725

ACC AGG CAC ACA GAC TTT GAG GAG AGG GCG TAT GTC GTC TTG ATC CGC     2322
Thr Arg His Thr Asp Phe Glu Glu Arg Ala Tyr Val Val Leu Ile Arg
730                     735                     740                     745

ATC AAT GAT GGG GGT CGG CCA CCC TTG GAA GGC ATT GTT TCT TTA CCA     2370
Ile Asn Asp Gly Gly Arg Pro Pro Leu Glu Gly Ile Val Ser Leu Pro
                    750                     755                     760

GTT ACA TTC TGC AGT TGT GTG GAA GGA AGT TGT TTC CGG CCA GCA GGT     2418
Val Thr Phe Cys Ser Cys Val Glu Gly Ser Cys Phe Arg Pro Ala Gly
                765                     770                     775
```

```
CAC CAG ACT GGG ATA CCC ACT GTG GGC ATG GCA GTT GGT ATA CTG CTG     2466
His Gln Thr Gly Ile Pro Thr Val Gly Met Ala Val Gly Ile Leu Leu
        780                 785                     790

ACC ACC CTT CTG GTG ATT GGT ATA ATT TTA GCA GTT GTG TTT ATC CGC     2514
Thr Thr Leu Leu Val Ile Gly Ile Ile Leu Ala Val Val Phe Ile Arg
    795                 800                     805

ATA AAG AAG GAT AAA GGC AAA GAT AAT GTT GAA AGT GCT CAA GCA TCT     2562
Ile Lys Lys Asp Lys Gly Lys Asp Asn Val Glu Ser Ala Gln Ala Ser
810                 815                     820                 825

GAA GTC AAA CCT CTG AGA AGC TGAATTTGAA AAGGAATGTT TGAATTTATA TAGC  2617
Glu Val Lys Pro Leu Arg Ser
                830

AAGTGCTATT TCAGCAACAA CCATCTCATC CTATTACTTT TCATCTAACG TGCATTATAA   2677
TTTTTTAAAC AGATATTCCC TCTTGTCCTT TAATATTTGC TAAATATTTC TTTTTTGAGG   2737
TGGAGTCTTG CTCTGTCGCC CAGGCTGGAG TACAGTGGTG TGATCCCAGC TCACTGCAAC   2797
CTCCGCCTCC TGGGTTCACA TGATTCTCCT GCCTCAGCTT CCTAAGTAGC TGGGTTTACA   2857
GGCACCCACC ACCATGCCCA GCTAATTTTT GTATTTTTAA TAGAGACGGG GTTTCGCCAT   2917
TTGGCCAGGC TGGTCTTGAA CTCCTGACGT CAAGTGATCT GCCTGCCTTG GTCTCCCAAT   2977
ACAGGCATGA ACCACTGCAC CCACCTACTT AGATATTTCA TGTGCTATAG ACATTAGAGA   3037
GATTTTTCAT TTTTCCATGA CATTTTTCCT CTCTGCAAAT GGCTTAGCTA CTTGTGTTTT   3097
TCCCTTTTGG GGCAAGACAG ACTCATTAAA TATTCTGTAC ATTTTTTCTT TATCAAGGAG   3157
ATATATCAGT GTTGTCTCAT AGAACTGCCT GGATTCCATT TATGTTTTTT CTGATTCCAT   3217
CCTGTGTCCC CTTCATCCTT GACTCCTTTG GTATTTCACT GAATTTCAAA CATTTGTCAG   3277
AGAAGAAAAA AGTGAGGACT CAGGAAAAAT AAATAAATAA AAGAACAGCC TTTTGCGGCC   3337
GCGAATTC                                                            3345
```

(2) INFORMATION FOR SEQ ID NO:178:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 832 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:178:

```
Met Ile Leu Gln Ala His Leu His Ser Leu Cys Leu Leu Met Leu Tyr
 1               5                  10                  15
Leu Ala Thr Gly Tyr Gly Gln Glu Gly Lys Phe Ser Gly Pro Leu Lys
            20                  25                  30
Pro Met Thr Phe Ser Ile Tyr Glu Gly Gln Glu Pro Ser Gln Ile Ile
        35                  40                  45
Phe Gln Phe Lys Ala Asn Pro Pro Ala Val Thr Phe Glu Leu Thr Gly
    50                  55                  60
Glu Thr Asp Asn Ile Phe Val Ile Glu Arg Glu Gly Leu Leu Tyr Tyr
65                  70                  75                  80
Asn Arg Ala Leu Asp Arg Glu Thr Arg Ser Thr His Asn Leu Gln Val
                85                  90                  95
Ala Ala Leu Asp Ala Asn Gly Ile Ile Val Glu Gly Pro Val Pro Ile
            100                 105                 110
Thr Ile Glu Val Lys Asp Ile Asn Asp Asn Arg Pro Thr Phe Leu Gln
        115                 120                 125
Ser Lys Tyr Glu Gly Ser Val Arg Gln Asn Ser Arg Pro Gly Lys Pro
    130                 135                 140
Phe Leu Tyr Val Asn Ala Thr Asp Leu Asp Asp Pro Ala Thr Pro Asn
145                 150                 155                 160
Gly Gln Leu Tyr Tyr Gln Ile Val Ile Gln Leu Pro Met Ile Asn Asn
                165                 170                 175
Val Met Tyr Phe Gln Ile Asn Asn Lys Thr Gly Ala Ile Ser Leu Thr
            180                 185                 190
```

```
Arg Glu Gly Ser Gln Glu Leu Asn Pro Ala Lys Asn Pro Ser Tyr Asn
        195                 200                 205
Leu Val Ile Ser Val Lys Asp Met Gly Gly Gln Ser Glu Asn Ser Phe
    210                 215                 220
Ser Asp Thr Thr Ser Val Asp Ile Ile Val Thr Glu Asn Ile Trp Lys
225                 230                 235                 240
Ala Pro Lys Pro Val Glu Met Val Glu Asn Ser Thr Asp Pro His Pro
                245                 250                 255
Ile Lys Ile Thr Gln Val Arg Trp Asn Asp Pro Gly Ala Gln Tyr Ser
            260                 265                 270
Leu Val Asp Lys Glu Lys Leu Pro Arg Phe Pro Phe Ser Ile Asp Gln
        275                 280                 285
Glu Gly Asp Ile Tyr Val Thr Gln Pro Leu Asp Arg Glu Glu Lys Asp
    290                 295                 300
Ala Tyr Val Phe Tyr Ala Val Ala Lys Asp Glu Tyr Gly Lys Pro Leu
305                 310                 315                 320
Ser Tyr Pro Leu Glu Ile His Val Lys Val Lys Asp Ile Asn Asp Asn
                325                 330                 335
Pro Pro Thr Cys Pro Ser Pro Val Thr Val Phe Glu Val Gln Glu Asn
            340                 345                 350
Glu Arg Leu Gly Asn Ser Ile Gly Thr Leu Thr Ala His Asp Arg Asp
        355                 360                 365
Glu Glu Asn Thr Ala Asn Ser Phe Leu Asn Tyr Arg Ile Val Glu Gln
    370                 375                 380
Thr Pro Lys Leu Pro Met Asp Gly Leu Phe Leu Ile Gln Thr Tyr Ala
385                 390                 395                 400
Gly Met Leu Gln Leu Ala Lys Gln Ser Leu Lys Lys Gln Asp Thr Pro
                405                 410                 415
Gln Tyr Asn Leu Thr Ile Glu Val Ser Asp Lys Asp Phe Lys Thr Leu
            420                 425                 430
Cys Phe Val Gln Ile Asn Val Ile Asp Ile Asn Asp Gln Ile Pro Ile
        435                 440                 445
Phe Glu Lys Ser Asp Tyr Gly Asn Leu Thr Leu Ala Glu Asp Thr Asn
    450                 455                 460
Ile Gly Ser Thr Ile Leu Thr Ile Gln Ala Thr Asp Ala Asp Glu Pro
465                 470                 475                 480
Phe Thr Gly Ser Ser Lys Ile Leu Tyr His Ile Ile Lys Gly Asp Ser
                485                 490                 495
Glu Gly Arg Leu Gly Val Asp Thr Asp Pro His Thr Asn Thr Gly Tyr
            500                 505                 510
Val Ile Ile Lys Lys Pro Leu Asp Phe Glu Thr Ala Ala Val Ser Asn
        515                 520                 525
Ile Val Phe Lys Ala Glu Asn Pro Glu Pro Leu Val Phe Gly Val Lys
    530                 535                 540
Tyr Asn Ala Ser Ser Phe Ala Lys Phe Thr Leu Ile Val Thr Asp Val
545                 550                 555                 560
Asn Glu Ala Pro Gln Phe Ser Gln His Val Phe Gln Ala Lys Val Ser
                565                 570                 575
Glu Asp Val Ala Ile Gly Thr Lys Val Gly Asn Val Thr Ala Lys Asp
            580                 585                 590
Pro Glu Gly Leu Asp Ile Ser Tyr Ser Leu Arg Gly Asp Thr Arg Gly
        595                 600                 605
Trp Leu Lys Ile Asp His Val Thr Gly Glu Ile Phe Ser Val Ala Pro
    610                 615                 620
Leu Asp Arg Glu Ala Gly Ser Pro Tyr Arg Val Gln Val Val Ala Thr
625                 630                 635                 640
Glu Val Gly Gly Ser Ser Leu Ser Ser Val Ser Glu Phe His Leu Ile
                645                 650                 655
Leu Met Asp Val Asn Asp Asn Pro Pro Arg Leu Ala Lys Asp Tyr Thr
            660                 665                 670
Gly Leu Phe Phe Cys His Pro Leu Ser Ala Pro Gly Ser Leu Ile Phe
        675                 680                 685
Glu Ala Thr Asp Asp Asp Gln His Leu Phe Arg Gly Pro His Phe Thr
    690                 695                 700
Phe Ser Leu Gly Ser Gly Ser Leu Gln Asn Asp Trp Glu Val Ser Lys
705                 710                 715                 720
```

```
Ile Asn Gly Thr His Ala Arg Leu Ser Thr Arg His Thr Asp Phe Glu
                725                 730                 735
Glu Arg Ala Tyr Val Val Leu Ile Arg Ile Asn Asp Gly Gly Arg Pro
            740                 745                 750
Pro Leu Glu Gly Ile Val Ser Leu Pro Val Thr Phe Cys Ser Cys Val
        755                 760                 765
Glu Gly Ser Cys Phe Arg Pro Ala Gly His Gln Thr Gly Ile Pro Thr
    770                 775                 780
Val Gly Met Ala Val Gly Ile Leu Leu Thr Thr Leu Leu Val Ile Gly
785                 790                 795                 800
Ile Ile Leu Ala Val Val Phe Ile Arg Ile Lys Lys Asp Lys Gly Lys
                805                 810                 815
Asp Asn Val Glu Ser Ala Gln Ala Ser Glu Val Lys Pro Leu Arg Ser
            820                 825                 830
```

(2) INFORMATION FOR SEQ ID NO:179:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1827 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:179:

```
Met Ala Arg Lys Lys Phe Ser Gly Leu Glu Ile Ser Leu Ile Val Leu
 1               5                  10                  15
Phe Val Ile Val Thr Ile Ile Ala Ile Ala Leu Ile Val Val Leu Ala
            20                  25                  30
Thr Lys Thr Pro Ala Val Asp Glu Ile Ser Asp Ser Thr Ser Thr Pro
        35                  40                  45
Ala Thr Thr Arg Val Thr Thr Asn Pro Ser Asp Ser Gly Lys Cys Pro
    50                  55                  60
Asn Val Leu Asn Asp Pro Val Asn Val Arg Ile Asn Cys Ile Pro Glu
65                  70                  75                  80
Gln Phe Pro Thr Glu Gly Ile Cys Ala Gln Arg Gly Cys Cys Trp Arg
                85                  90                  95
Pro Trp Asn Asp Ser Leu Ile Pro Trp Cys Phe Phe Val Asp Asn His
            100                 105                 110
Gly Tyr Asn Val Gln Asp Met Thr Thr Thr Ser Ile Gly Val Glu Ala
        115                 120                 125
Lys Leu Asn Arg Ile Pro Ser Pro Thr Leu Phe Gly Asn Asp Ile Asn
    130                 135                 140
Ser Val Leu Phe Thr Thr Gln Asn Gln Thr Pro Asn Arg Phe Arg Phe
145                 150                 155                 160
Lys Ile Thr Asp Pro Asn Asn Arg Arg Tyr Glu Val Pro His Gln Tyr
                165                 170                 175
Val Lys Glu Phe Thr Gly Pro Thr Val Ser Asp Thr Leu Tyr Asp Val
            180                 185                 190
Lys Val Ala Gln Asn Pro Phe Ser Ile Gln Val Ile Arg Lys Ser Asn
        195                 200                 205
Gly Lys Thr Leu Phe Asp Thr Ser Ile Gly Pro Leu Val Tyr Ser Asp
    210                 215                 220
Gln Tyr Leu Gln Ile Ser Ala Arg Leu Pro Ser Asp Tyr Ile Tyr Gly
225                 230                 235                 240
Ile Gly Glu Gln Val His Lys Arg Phe Arg His Asp Leu Ser Trp Lys
                245                 250                 255
Thr Trp Pro Ile Phe Thr Arg Asp Gln Leu Pro Gly Asp Asn Asn Asn
            260                 265                 270
Asn Leu Tyr Gly His Gln Thr Phe Phe Met Cys Ile Glu Asp Thr Ser
        275                 280                 285
Gly Lys Ser Phe Gly Val Phe Leu Met Asn Ser Asn Ala Met Glu Ile
    290                 295                 300
Phe Ile Gln Pro Thr Pro Ile Val Thr Tyr Arg Val Thr Gly Gly Ile
```

305 310 315 320
Leu Asp Phe Tyr Ile Leu Leu Gly Asp Thr Pro Glu Gln Val Val Gln
325 330 335
Gln Tyr Gln Gln Leu Val Gly Leu Pro Ala Met Pro Ala Tyr Trp Asn
340 345 350
Leu Gly Phe Gln Leu Ser Arg Trp Asn Tyr Lys Ser Leu Asp Val Val
355 360 365
Lys Glu Val Val Arg Arg Asn Arg Glu Ala Gly Ile Pro Phe Asp Thr
370 375 380
Gln Val Thr Asp Ile Asp Tyr Met Glu Asp Lys Lys Asp Phe Thr Tyr
385 390 395 400
Asp Gln Val Ala Phe Asn Gly Leu Pro Gln Phe Val Gln Asp Leu His
405 410 415
Asp His Gly Gln Lys Tyr Val Ile Ile Leu Asp Pro Ala Ile Ser Ile
420 425 430
Gly Arg Arg Ala Asn Gly Thr Thr Tyr Ala Thr Tyr Glu Arg Gly Asn
435 440 445
Thr Gln His Val Trp Ile Asn Glu Ser Asp Gly Ser Thr Pro Ile Ile
450 455 460
Gly Glu Val Trp Pro Gly Leu Thr Val Tyr Pro Asp Phe Thr Asn Pro
465 470 475 480
Asn Cys Ile Asp Trp Trp Ala Asn Glu Cys Ser Ile Phe His Gln Glu
485 490 495
Val Gln Tyr Asp Gly Leu Trp Ile Asp Met Asn Glu Val Ser Ser Phe
500 505 510
Ile Gln Gly Ser Thr Lys Gly Cys Asn Val Asn Lys Leu Asn Tyr Pro
515 520 525
Pro Phe Thr Pro Asp Ile Leu Asp Lys Leu Met Tyr Ser Lys Thr Ile
530 535 540
Cys Met Asp Ala Val Gln Asn Trp Gly Lys Gln Tyr Asp Val His Ser
545 550 555 560
Leu Tyr Gly Tyr Ser Met Ala Ile Ala Thr Glu Gln Ala Val Gln Lys
565 570 575
Val Phe Pro Asn Lys Arg Ser Phe Ile Leu Thr Arg Ser Thr Phe Ala
580 585 590
Gly Ser Gly Arg His Ala Ala His Trp Leu Gly Asp Asn Thr Ala Ser
595 600 605
Trp Glu Gln Met Glu Trp Ser Ile Thr Gly Met Leu Glu Phe Ser Leu
610 615 620
Phe Gly Ile Pro Leu Val Gly Ala Asp Ile Cys Gly Phe Val Ala Glu
625 630 635 640
Thr Thr Glu Glu Leu Cys Arg Arg Trp Met Gln Leu Gly Ala Phe Tyr
645 650 655
Pro Phe Ser Arg Asn His Asn Ser Asp Gly Tyr Glu His Gln Asp Pro
660 665 670
Ala Phe Phe Gly Gln Asn Ser Leu Leu Val Lys Ser Ser Arg Gln Tyr
675 680 685
Leu Thr Ile Arg Tyr Thr Leu Leu Pro Phe Leu Tyr Thr Leu Phe Tyr
690 695 700
Lys Ala His Val Phe Gly Glu Thr Val Ala Arg Pro Val Leu His Glu
705 710 715 720
Phe Tyr Glu Asp Thr Asn Ser Trp Ile Glu Asp Thr Glu Phe Leu Trp
725 730 735
Gly Pro Ala Leu Leu Ile Thr Pro Val Leu Lys Gln Gly Ala Asp Thr
740 745 750
Val Ser Ala Tyr Ile Pro Asp Ala Ile Trp Tyr Asp Tyr Glu Ser Gly
755 760 765
Ala Lys Arg Pro Trp Arg Lys Gln Arg Val Asp Met Tyr Leu Pro Ala
770 775 780
Asp Lys Ile Gly Leu His Leu Arg Gly Gly Tyr Ile Ile Pro Ile Gln
785 790 795 800
Glu Pro Asp Val Thr Thr Thr Ala Ser Arg Lys Asn Pro Leu Gly Leu
805 810 815
Ile Val Ala Leu Gly Glu Asn Asn Thr Ala Lys Gly Asp Phe Phe Trp
820 825 830
Asp Asp Gly Glu Thr Lys Asp Thr Ile Gln Asn Gly Asn Tyr Ile Leu

```
            835                 840                 845
    Tyr Thr Phe Ser Val Ser Asn Asn Thr Leu Asp Ile Val Cys Thr His
        850                 855                 860
    Ser Ser Tyr Gln Glu Gly Thr Thr Leu Ala Phe Gln Thr Val Lys Ile
    865                 870                 875                 880
    Leu Gly Leu Thr Asp Ser Val Thr Glu Val Arg Val Ala Glu Asn Asn
                    885                 890                 895
    Gln Pro Met Asn Ala His Ser Asn Phe Thr Tyr Asp Ala Ser Asn Gln
                900                 905                 910
    Val Leu Leu Ile Ala Asp Leu Lys Leu Asn Leu Gly Arg Asn Phe Ser
            915                 920                 925
    Val Gln Trp Asn Gln Ile Phe Ser Glu Asn Glu Arg Phe Asn Cys Tyr
        930                 935                 940
    Pro Asp Ala Asp Leu Ala Thr Glu Gln Lys Cys Thr Gln Arg Gly Cys
    945                 950                 955                 960
    Val Trp Arg Thr Gly Ser Ser Leu Ser Lys Ala Pro Glu Cys Tyr Phe
                    965                 970                 975
    Pro Arg Gln Asp Asn Ser Tyr Ser Val Asn Ser Ala Arg Tyr Ser Ser
                980                 985                 990
    Met Gly Ile Thr Ala Asp Leu Gln Leu Asn Thr Ala Asn Ala Arg Ile
            995                 1000                1005
    Lys Leu Pro Ser Asp Pro Ile Ser Thr Leu Arg Val Glu Val Lys Tyr
        1010                1015                1020
    His Lys Asn Asp Met Leu Gln Phe Lys Ile Tyr Asp Pro Gln Lys Lys
    025                 1030                1035                1040
    Arg Tyr Glu Val Pro Val Pro Leu Asn Ile Pro Thr Thr Pro Ile Ser
                    1045                1050                1055
    Thr Tyr Glu Asp Arg Leu Tyr Asp Val Glu Ile Lys Glu Asn Pro Phe
                1060                1065                1070
    Gly Ile Gln Ile Arg Arg Arg Ser Ser Gly Arg Val Ile Trp Asp Ser
            1075                1080                1085
    Trp Leu Pro Gly Phe Ala Phe Asn Asp Gln Phe Ile Gln Ile Ser Thr
        1090                1095                1100
    Arg Leu Pro Ser Glu Tyr Ile Tyr Gly Phe Gly Glu Val Glu His Thr
    105                 1110                1115                1120
    Ala Phe Lys Arg Asp Leu Asn Trp Asn Thr Trp Gly Met Phe Thr Arg
                    1125                1130                1135
    Asp Gln Pro Pro Gly Tyr Lys Leu Asn Ser Tyr Gly Phe His Pro Tyr
                1140                1145                1150
    Tyr Met Ala Leu Glu Glu Glu Gly Asn Ala His Gly Val Phe Leu Leu
            1155                1160                1165
    Asn Ser Asn Ala Met Asp Val Thr Phe Gln Pro Thr Pro Ala Leu Thr
        1170                1175                1180
    Tyr Arg Thr Val Gly Gly Ile Leu Asp Phe Tyr Met Phe Leu Gly Pro
    185                 1190                1195                1200
    Thr Pro Gln Val Ala Thr Lys Gln Tyr His Glu Val Ile Gly His Pro
                    1205                1210                1215
    Val Met Pro Ala Tyr Trp Ala Leu Gly Phe Gln Leu Cys Arg Tyr Gly
                1220                1225                1230
    Tyr Ala Asn Thr Ser Glu Val Arg Glu Leu Tyr Asp Ala Met Val Ala
            1235                1240                1245
    Ala Asn Ile Pro Tyr Asp Val Gln Tyr Thr Asp Ile Asp Tyr Met Glu
        1250                1255                1260
    Arg Gln Leu Asp Phe Thr Ile Gly Glu Ala Phe Gln Asp Leu Pro Gln
    265                 1270                1275                1280
    Phe Val Asp Lys Ile Arg Gly Glu Gly Met Arg Tyr Ile Ile Ile Leu
                    1285                1290                1295
    Asp Pro Ala Ile Ser Gly Asn Glu Thr Lys Thr Tyr Pro Ala Phe Glu
                1300                1305                1310
    Arg Gly Gln Gln Asn Asp Val Phe Val Lys Trp Pro Asn Thr Asn Asp
            1315                1320                1325
    Ile Cys Trp Ala Lys Val Trp Pro Asp Leu Pro Asn Ile Thr Ile Asp
        1330                1335                1340
    Lys Thr Leu Thr Glu Asp Glu Ala Val Asn Ala Ser Arg Ala His Val
    345                 1350                1355                1360
    Ala Phe Pro Asp Phe Phe Arg Thr Ser Thr Ala Glu Trp Trp Ala Arg
```

```
                  1365                          1370                          1375
Glu Ile Val Asp Phe Tyr Asn Glu Lys Met Lys Phe Asp Gly Leu Trp
              1380                          1385                          1390
Ile Asp Met Asn Glu Pro Ser Ser Phe Val Asn Gly Thr Thr Thr Asn
          1395                          1400                          1405
Gln Cys Arg Asn Asp Glu Leu Asn Tyr Pro Pro Tyr Phe Pro Glu Leu
      1410                          1415                          1420
Thr Lys Arg Thr Asp Gly Leu His Phe Arg Thr Ile Cys Met Glu Ala
425                           1430                          1435                          1440
Glu Gln Ile Leu Ser Asp Gly Thr Ser Val Leu His Tyr Asp Val His
                  1445                          1450                          1455
Asn Leu Tyr Gly Trp Ser Gln Met Lys Pro Thr His Asp Ala Leu Gln
              1460                          1465                          1470
Lys Thr Thr Gly Lys Arg Gly Ile Val Ile Ser Arg Ser Thr Tyr Pro
          1475                          1480                          1485
Thr Ser Gly Arg Trp Gly Gly His Trp Leu Gly Asp Asn Tyr Ala Arg
      1490                          1495                          1500
Trp Asp Asn Met Asp Lys Ser Ile Ile Gly Met Met Glu Phe Ser Leu
505                           1510                          1515                          1520
Phe Gly Ile Ser Tyr Thr Gly Ala Asp Ile Cys Gly Phe Phe Asn Asn
                  1525                          1530                          1535
Ser Glu Tyr His Leu Cys Thr Arg Trp Met Gln Leu Gly Ala Phe Tyr
              1540                          1545                          1550
Pro Tyr Ser Arg Asn His Asn Ile Ala Asn Thr Arg Arg Gln Asp Pro
          1555                          1560                          1565
Ala Ser Trp Asn Glu Thr Phe Ala Glu Met Ser Arg Asn Ile Leu Asn
      1570                          1575                          1580
Ile Arg Tyr Thr Leu Leu Pro Tyr Phe Tyr Thr Gln Met His Glu Ile
585                           1590                          1595                          1600
His Ala Asn Gly Gly Thr Val Ile Arg Pro Leu Leu His Glu Phe Phe
                  1605                          1610                          1615
Asp Glu Lys Pro Thr Trp Asp Ile Phe Lys Gln Phe Leu Trp Gly Pro
              1620                          1625                          1630
Ala Phe Met Val Thr Pro Val Leu Glu Pro Tyr Val Gln Thr Val Asn
          1635                          1640                          1645
Ala Tyr Val Pro Asn Ala Arg Trp Phe Asp Tyr His Thr Gly Lys Asp
      1650                          1655                          1660
Ile Gly Val Arg Gly Gln Phe Gln Thr Phe Asn Ala Ser Tyr Asp Thr
665                           1670                          1675                          1680
Ile Asn Leu His Val Arg Gly Gly His Ile Leu Pro Cys Gln Glu Pro
                  1685                          1690                          1695
Ala Gln Asn Thr Phe Tyr Ser Arg Gln Lys His Met Lys Leu Ile Val
              1700                          1705                          1710
Ala Ala Asp Asp Asn Gln Met Ala Gln Gly Ser Leu Phe Trp Asp Asp
          1715                          1720                          1725
Gly Glu Ser Ile Asp Thr Tyr Glu Arg Asp Leu Tyr Leu Ser Val Gln
      1730                          1735                          1740
Phe Asn Leu Asn Gln Thr Thr Leu Thr Ser Thr Ile Leu Lys Arg Gly
745                           1750                          1755                          1760
Tyr Ile Asn Lys Ser Glu Thr Arg Leu Gly Ser Leu His Val Trp Gly
                  1765                          1770                          1775
Lys Gly Thr Thr Pro Val Asn Ala Val Thr Leu Thr Tyr Asn Gly Asn
              1780                          1785                          1790
Lys Asn Ser Leu Pro Phe Asn Glu Asp Thr Thr Asn Met Ile Leu Arg
          1795                          1800                          1805
Ile Asp Leu Thr Thr His Asn Val Thr Leu Glu Glu Pro Ile Glu Ile
      1810                          1815                          1820
Asn Trp Ser
825
```

(2) INFORMATION FOR SEQ ID NO:180:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2284 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 45...2099
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:180:

```
GCCTTACTGC AGGAAGGCAC TCCGAAGACA TAAGTCGGTG AGAC ATG GCT GAA GAT     56
                                                 Met Ala Glu Asp
                                                  1

AAA AGC AAG AGA GAC TCC ATC GAG ATG AGT ATG AAG GGA TGC CAG ACA     104
Lys Ser Lys Arg Asp Ser Ile Glu Met Ser Met Lys Gly Cys Gln Thr
 5                  10                  15                  20

AAC AAC GGG TTT GTC CAT AAT GAA GAC ATT CTG GAG CAG ACC CCG GAT     152
Asn Asn Gly Phe Val His Asn Glu Asp Ile Leu Glu Gln Thr Pro Asp
                25                  30                  35

CCA GGC AGC TCA ACA GAC AAC CTG AAG CAC AGC ACC AGG GGC ATC CTT     200
Pro Gly Ser Ser Thr Asp Asn Leu Lys His Ser Thr Arg Gly Ile Leu
            40                  45                  50

GGC TCC CAG GAG CCC GAC TTC AAG GGC GTC CAG CCC TAT GCG GGG ATG     248
Gly Ser Gln Glu Pro Asp Phe Lys Gly Val Gln Pro Tyr Ala Gly Met
        55                  60                  65

CCC AAG GAG GTG CTG TTC CAG TTC TCT GGC CAG GCC CGC TAC CGC ATA     296
Pro Lys Glu Val Leu Phe Gln Phe Ser Gly Gln Ala Arg Tyr Arg Ile
    70                  75                  80

CCT CGG GAG ATC CTC TTC TGG CTC ACA GTG GCT TCT GTG CTG GTG CTC     344
Pro Arg Glu Ile Leu Phe Trp Leu Thr Val Ala Ser Val Leu Val Leu
85                  90                  95                  100

ATC GCG GCC ACC ATA GCC ATC ATT GCC CTC TCT CCA AAG TGC CTA GAC     392
Ile Ala Ala Thr Ile Ala Ile Ile Ala Leu Ser Pro Lys Cys Leu Asp
                105                 110                 115

TGG TGG CAG GAG GGG CCC ATG TAC CAG ATC TAC CCA AGG TCT TTC AAG     440
Trp Trp Gln Glu Gly Pro Met Tyr Gln Ile Tyr Pro Arg Ser Phe Lys
            120                 125                 130

GAC AGT AAC AAG GAT GGG AAC GGA GAT CTG AAA GGT ATT CAA GAT AAA     488
Asp Ser Asn Lys Asp Gly Asn Gly Asp Leu Lys Gly Ile Gln Asp Lys
        135                 140                 145

CTG GAC TAC ATC ACA GCT TTA AAT ATA AAA ACT GTT TGG ATT ACT TCA     536
Leu Asp Tyr Ile Thr Ala Leu Asn Ile Lys Thr Val Trp Ile Thr Ser
    150                 155                 160

TTT TAT AAA TCG TCC CTT AAA GAT TTC AGA TAT GGT GTT GAA GAT TTC     584
Phe Tyr Lys Ser Ser Leu Lys Asp Phe Arg Tyr Gly Val Glu Asp Phe
165                 170                 175                 180

CGG GAA GTT GAT CCC ATT TTT GGA ACG ATG GAA GAT TTT GAG AAT CTG     632
Arg Glu Val Asp Pro Ile Phe Gly Thr Met Glu Asp Phe Glu Asn Leu
                185                 190                 195

GTT GCA GCC ATA CAT GAT AAA GGT TTA AAA TTA ATC ATC GAT TTC ATA     680
Val Ala Ala Ile His Asp Lys Gly Leu Lys Leu Ile Ile Asp Phe Ile
```

```
                200                      205                      210

CCA AAC CAC ACG AGT GAT AAA CAT ATT TGG TTT CAA TTG AGT CGG ACA      728
Pro Asn His Thr Ser Asp Lys His Ile Trp Phe Gln Leu Ser Arg Thr
        215                     220                     225

CGG ACA GGA AAA TAT ACT GAT TAT TAT ATC TGG CAT GAC TGT ACC CAT      776
Arg Thr Gly Lys Tyr Thr Asp Tyr Tyr Ile Trp His Asp Cys Thr His
    230                     235                     240

GAA AAT GGC AAA ACC ATT CCA CCC AAC AAC TGG TTA AGT GTG TAT GGA      824
Glu Asn Gly Lys Thr Ile Pro Pro Asn Asn Trp Leu Ser Val Tyr Gly
245                     250                     255                 260

AAC TCC AGT TGG CAC TTT GAC GAA GTG CGA AAC CAA TGT TAT TTT CAT      872
Asn Ser Ser Trp His Phe Asp Glu Val Arg Asn Gln Cys Tyr Phe His
                265                     270                     275

CAG TTT ATG AAA GAG CAA CCT GAT TTA AAT TTC CGC AAT CCT GAT GTT      920
Gln Phe Met Lys Glu Gln Pro Asp Leu Asn Phe Arg Asn Pro Asp Val
            280                     285                     290

CAA GAA GAA ATA AAA GAA ATT TTA CGG TTC TGG CTC ACA AAG GGT GTT      968
Gln Glu Glu Ile Lys Glu Ile Leu Arg Phe Trp Leu Thr Lys Gly Val
        295                     300                     305

GAT GGT TTT AGT TTG GAT GCT GTT AAA TTC CTC CTA GAA GCA AAG CAC     1016
Asp Gly Phe Ser Leu Asp Ala Val Lys Phe Leu Leu Glu Ala Lys His
    310                     315                     320

CTG AGA GAT GAG ATC CAA GTA AAT AAG ACC CAA ATC CCG GAC ACG GTC     1064
Leu Arg Asp Glu Ile Gln Val Asn Lys Thr Gln Ile Pro Asp Thr Val
325                     330                     335                 340

ACA CAA TAC TCG GAG CTG TAC CAT GAC TTC ACC ACC ACG CAG GTG GGA     1112
Thr Gln Tyr Ser Glu Leu Tyr His Asp Phe Thr Thr Thr Gln Val Gly
                345                     350                     355

ATG CAC GAC ATT GTC CGC AGC TTC CGG CAG ACC ATG GAC CAA TAC AGC     1160
Met His Asp Ile Val Arg Ser Phe Arg Gln Thr Met Asp Gln Tyr Ser
            360                     365                     370

ACG GAG CCC GGC AGA TAC AGG TTC ATG GGG ACT GAA GCC TAT GCA GAG     1208
Thr Glu Pro Gly Arg Tyr Arg Phe Met Gly Thr Glu Ala Tyr Ala Glu
        375                     380                     385

AGT ATT GAC AGG ACC GTG ATG TAC TAT GGA TTG CCA TTT ATC CAA GAA     1256
Ser Ile Asp Arg Thr Val Met Tyr Tyr Gly Leu Pro Phe Ile Gln Glu
    390                     395                     400

GCT GAT TTT CCC TTC AAC AAT TAC CTC AGC ATG CTA GAC ACT GTT TCT     1304
Ala Asp Phe Pro Phe Asn Asn Tyr Leu Ser Met Leu Asp Thr Val Ser
405                     410                     415                 420

GGG AAC AGC GTG TAT GAG GTT ATC ACA TCC TGG ATG GAA AAC ATG CCA     1352
Gly Asn Ser Val Tyr Glu Val Ile Thr Ser Trp Met Glu Asn Met Pro
                425                     430                     435

GAA GGA AAA TGG CCT AAC TGG ATG ATT GGT GGA CCA GAC AGT TCA CGG     1400
Glu Gly Lys Trp Pro Asn Trp Met Ile Gly Gly Pro Asp Ser Ser Arg
            440                     445                     450

CTG ACT TCG CGT TTG GGG AAT CAG TAT GTC AAC GTG ATG AAC ATG CTT     1448
Leu Thr Ser Arg Leu Gly Asn Gln Tyr Val Asn Val Met Asn Met Leu
        455                     460                     465
```

```
CTT TTC ACA CTC CCT GGA ACT CCT ATA ACT TAC TAT GGA GAA GAA ATT      1496
Leu Phe Thr Leu Pro Gly Thr Pro Ile Thr Tyr Tyr Gly Glu Glu Ile
    470                 475                 480

GGA ATG GGA AAT ATT GTA GCC GCA AAT CTC AAT GAA AGC TAT GAT ATT      1544
Gly Met Gly Asn Ile Val Ala Ala Asn Leu Asn Glu Ser Tyr Asp Ile
485                 490                 495                 500

AAT ACC CTT CGC TCA AAG TCA CCA ATG CAG TGG GAC AAT AGT TCA AAT      1592
Asn Thr Leu Arg Ser Lys Ser Pro Met Gln Trp Asp Asn Ser Ser Asn
                505                 510                 515

GCT GGT TTT TCT GAA GCT AGT AAC ACC TGG TTA CCT ACC AAT TCA GAT      1640
Ala Gly Phe Ser Glu Ala Ser Asn Thr Trp Leu Pro Thr Asn Ser Asp
            520                 525                 530

TAC CAC ACT GTG AAT GTT GAT GTC CAA AAG ACT CAG CCC AGA TCG GCT      1688
Tyr His Thr Val Asn Val Asp Val Gln Lys Thr Gln Pro Arg Ser Ala
        535                 540                 545

TTG AAG TTA TAT CAA GAT TTA AGT CTA CTT CAT GCC AAT GAG CTA CTC      1736
Leu Lys Leu Tyr Gln Asp Leu Ser Leu Leu His Ala Asn Glu Leu Leu
    550                 555                 560

CTC AAC AGG GGC TGG TTT TGC CAT TTG AGG AAT GAC AGC CAC TAT GTT      1784
Leu Asn Arg Gly Trp Phe Cys His Leu Arg Asn Asp Ser His Tyr Val
565                 570                 575                 580

GTG TAC ACA AGA GAG CTG GAT GGC ATC GAC AGA ATC TTT ATC GTG GTT      1832
Val Tyr Thr Arg Glu Leu Asp Gly Ile Asp Arg Ile Phe Ile Val Val
                585                 590                 595

CTG AAT TTT GGA GAA TCA ACA CTG TTA AAT CTA CAT AAT ATG ATT TCG      1880
Leu Asn Phe Gly Glu Ser Thr Leu Leu Asn Leu His Asn Met Ile Ser
            600                 605                 610

GGC CTT CCC GCT AAA ATA AGA ATA AGG TTA AGT ACC AAT TCT GCC GAC      1928
Gly Leu Pro Ala Lys Ile Arg Ile Arg Leu Ser Thr Asn Ser Ala Asp
        615                 620                 625

AAA GGC AGT AAA GTT GAT ACA AGT GGC ATT TTT CTG GAC AAG GGA GAG      1976
Lys Gly Ser Lys Val Asp Thr Ser Gly Ile Phe Leu Asp Lys Gly Glu
    630                 635                 640

GGA CTC ATC TTT GAA CAC AAC ACG AAG AAT CTC CTT CAT CGC CAA ACA      2024
Gly Leu Ile Phe Glu His Asn Thr Lys Asn Leu Leu His Arg Gln Thr
645                 650                 655                 660

GCT TTC AGA GAT AGA TGC TTT GTT TCC AAT CGA GCA TGC TAT TCC AGT      2072
Ala Phe Arg Asp Arg Cys Phe Val Ser Asn Arg Ala Cys Tyr Ser Ser
                665                 670                 675

GTA CTG AAC ATA CTG TAT ACC TCG TGT TAGGCACCTT TATGAAGAGA TGAAGAC    2126
Val Leu Asn Ile Leu Tyr Thr Ser Cys
            680                 685

ACTGGCATTT CAGTGGGATT GTAAGCATTT GTAATAGCTT CATGTACAGC ATGCTGCTTG   2186
GTGAACAATC ATTAATTCTT CGATATTTCT GTAGCTTGAA TGTAACCGCT TTAAGAAAGG   2246
TTCTCAAATG TTTTGAAAAA AATAAAATGT TTAAAAGT                           2284
```

(2) INFORMATION FOR SEQ ID NO:181:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 685 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:181:

```
Met Ala Glu Asp Lys Ser Lys Arg Asp Ser Ile Glu Met Ser Met Lys
 1               5                  10                  15
Gly Cys Gln Thr Asn Asn Gly Phe Val His Asn Glu Asp Ile Leu Glu
            20                  25                  30
Gln Thr Pro Asp Pro Gly Ser Ser Thr Asp Asn Leu Lys His Ser Thr
        35                  40                  45
Arg Gly Ile Leu Gly Ser Gln Glu Pro Asp Phe Lys Gly Val Gln Pro
    50                  55                  60
Tyr Ala Gly Met Pro Lys Glu Val Leu Phe Gln Phe Ser Gly Gln Ala
65                  70                  75                  80
Arg Tyr Arg Ile Pro Arg Glu Ile Leu Phe Trp Leu Thr Val Ala Ser
                85                  90                  95
Val Leu Val Leu Ile Ala Ala Thr Ile Ala Ile Ile Ala Leu Ser Pro
            100                 105                 110
Lys Cys Leu Asp Trp Trp Gln Glu Gly Pro Met Tyr Gln Ile Tyr Pro
        115                 120                 125
Arg Ser Phe Lys Asp Ser Asn Lys Asp Gly Asn Gly Asp Leu Lys Gly
    130                 135                 140
Ile Gln Asp Lys Leu Asp Tyr Ile Thr Ala Leu Asn Ile Lys Thr Val
145                 150                 155                 160
Trp Ile Thr Ser Phe Tyr Lys Ser Ser Leu Lys Asp Phe Arg Tyr Gly
                165                 170                 175
Val Glu Asp Phe Arg Glu Val Asp Pro Ile Phe Gly Thr Met Glu Asp
            180                 185                 190
Phe Glu Asn Leu Val Ala Ala Ile His Asp Lys Gly Leu Lys Leu Ile
        195                 200                 205
Ile Asp Phe Ile Pro Asn His Thr Ser Asp Lys His Ile Trp Phe Gln
    210                 215                 220
Leu Ser Arg Thr Arg Thr Gly Lys Tyr Thr Asp Tyr Tyr Ile Trp His
225                 230                 235                 240
Asp Cys Thr His Glu Asn Gly Lys Thr Ile Pro Pro Asn Asn Trp Leu
                245                 250                 255
Ser Val Tyr Gly Asn Ser Ser Trp His Phe Asp Glu Val Arg Asn Gln
            260                 265                 270
Cys Tyr Phe His Gln Phe Met Lys Glu Gln Pro Asp Leu Asn Phe Arg
        275                 280                 285
Asn Pro Asp Val Gln Glu Glu Ile Lys Glu Ile Leu Arg Phe Trp Leu
    290                 295                 300
Thr Lys Gly Val Asp Gly Phe Ser Leu Asp Ala Val Lys Phe Leu Leu
305                 310                 315                 320
Glu Ala Lys His Leu Arg Asp Glu Ile Gln Val Asn Lys Thr Gln Ile
                325                 330                 335
Pro Asp Thr Val Thr Gln Tyr Ser Glu Leu Tyr His Asp Phe Thr Thr
            340                 345                 350
Thr Gln Val Gly Met His Asp Ile Val Arg Ser Phe Arg Gln Thr Met
        355                 360                 365
Asp Gln Tyr Ser Thr Glu Pro Gly Arg Tyr Arg Phe Met Gly Thr Glu
    370                 375                 380
Ala Tyr Ala Glu Ser Ile Asp Arg Thr Val Met Tyr Tyr Gly Leu Pro
385                 390                 395                 400
Phe Ile Gln Glu Ala Asp Phe Pro Phe Asn Asn Tyr Leu Ser Met Leu
                405                 410                 415
Asp Thr Val Ser Gly Asn Ser Val Tyr Glu Val Ile Thr Ser Trp Met
            420                 425                 430
Glu Asn Met Pro Glu Gly Lys Trp Pro Asn Trp Met Ile Gly Gly Pro
        435                 440                 445
Asp Ser Ser Arg Leu Thr Ser Arg Leu Gly Asn Gln Tyr Val Asn Val
    450                 455                 460
Met Asn Met Leu Leu Phe Thr Leu Pro Gly Thr Pro Ile Thr Tyr Tyr
465                 470                 475                 480
```

```
Gly Glu Glu Ile Gly Met Gly Asn Ile Val Ala Ala Asn Leu Asn Glu
                485                 490                 495
Ser Tyr Asp Ile Asn Thr Leu Arg Ser Lys Ser Pro Met Gln Trp Asp
            500                 505                 510
Asn Ser Ser Asn Ala Gly Phe Ser Glu Ala Ser Asn Thr Trp Leu Pro
        515                 520                 525
Thr Asn Ser Asp Tyr His Thr Val Asn Val Asp Val Gln Lys Thr Gln
    530                 535                 540
Pro Arg Ser Ala Leu Lys Leu Tyr Gln Asp Leu Ser Leu Leu His Ala
545                 550                 555                 560
Asn Glu Leu Leu Leu Asn Arg Gly Trp Phe Cys His Leu Arg Asn Asp
                565                 570                 575
Ser His Tyr Val Val Tyr Thr Arg Glu Leu Asp Gly Ile Asp Arg Ile
            580                 585                 590
Phe Ile Val Val Leu Asn Phe Gly Glu Ser Thr Leu Leu Asn Leu His
        595                 600                 605
Asn Met Ile Ser Gly Leu Pro Ala Lys Ile Arg Ile Arg Leu Ser Thr
    610                 615                 620
Asn Ser Ala Asp Lys Gly Ser Lys Val Asp Thr Ser Gly Ile Phe Leu
625                 630                 635                 640
Asp Lys Gly Glu Gly Leu Ile Phe Glu His Asn Thr Lys Asn Leu Leu
                645                 650                 655
His Arg Gln Thr Ala Phe Arg Asp Arg Cys Phe Val Ser Asn Arg Ala
            660                 665                 670
Cys Tyr Ser Ser Val Leu Asn Ile Leu Tyr Thr Ser Cys
        675                 680                 685
```

(2) INFORMATION FOR SEQ ID NO:182:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:182:

```
Leu Val Pro Arg Gly Ser Pro Gly Ile Pro Gly Ser Arg Val Gly Gln
1               5                   10                  15
Cys Thr Asp Ser Asp Val Arg Arg Pro Trp Ala Arg Ser Cys Ala His
            20                  25                  30
Gln Gly Cys Gly Ala Gly Thr Arg Asn Ser His Gly Cys Ile Thr Arg
        35                  40                  45
Pro Leu Arg Gln Ala Ser
    50
```

(2) INFORMATION FOR SEQ ID NO:183:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:183:

```
Ser Ala Arg Asp Ser Gly Pro Ala Glu Asp Gly Ser Arg Ala Val Arg
1               5                   10                  15
Leu Asn Gly
```

(2) INFORMATION FOR SEQ ID NO:184:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:184:

```
Asp Gly Ser Arg Ala Val Arg Leu Asn Gly Val Glu Asn Ala Asn Thr
 1               5                  10                  15
Arg Lys Ser Ser Arg
            20
```

(2) INFORMATION FOR SEQ ID NO:185:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:185:

```
Glu Asn Ala Asn Thr Arg Lys Ser Ser Arg Ser Asn Pro Arg Gly Arg
 1               5                  10                  15
Arg His Pro
```

(2) INFORMATION FOR SEQ ID NO:186:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:186:

```
Thr Arg Lys Ser Ser Arg Ser Asn Pro Arg Gly
 1               5                  10
```

(2) INFORMATION FOR SEQ ID NO:187:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:187:

```
Ser Arg Pro Tyr Ser Val Asp Ser Asp Ser Asp Thr Asn Ala Lys His
 1               5                  10                  15
Ser Ser His Asn Arg
            20
```

(2) INFORMATION FOR SEQ ID NO:188:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:188:

```
Thr Asn Ala Lys His Ser Ser His Asn Arg Arg Leu Arg Thr Arg Ser
 1              5                  10                  15
Arg Pro Asn
```

(2) INFORMATION FOR SEQ ID NO:189:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:189:

```
Arg Tyr Lys His Asp Ile Gly Cys Asp Ala Gly Val Asp Lys Lys Ser
 1              5                  10                  15
Ser Ser Val Arg Gly Gly Cys Gly
            20
```

(2) INFORMATION FOR SEQ ID NO:190:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:190:

```
Gly Cys Asp Ala Gly Val Asp Lys Lys Ser Ser Ser Val Arg Gly Gly
 1              5                  10                  15
Cys Gly Ala His Ser Ser Pro Pro Arg Ala
            20                  25
```

(2) INFORMATION FOR SEQ ID NO:191:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:191:

```
Gly Ala His Ser Ser Pro Pro Arg Ala Gly Arg Gly Pro Arg Gly Thr
 1              5                  10                  15
Met Val Ser Arg Leu
            20
```

(2) INFORMATION FOR SEQ ID NO:192:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:192:

```
Glu Asn Ala Asn Thr Arg Lys Ser Ser Arg
 1               5                  10
```

(2) INFORMATION FOR SEQ ID NO:193:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:193:

```
Lys Lys Arg Ile Ala Gly Leu Pro Trp Tyr Arg Cys Arg Thr Val Ala
 1               5                  10                  15
Phe Glu Thr Gly Met Gln Asn Thr Gln Leu Cys Ser Thr Ile Val Gln
            20                  25                  30
Leu Ser Phe Thr Pro Glu Glu
        35
```

(2) INFORMATION FOR SEQ ID NO:194:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:194:

```
Arg Lys Ser Ser Arg Ser Asn Pro Arg Gly
 1               5                  10
```

(2) INFORMATION FOR SEQ ID NO:195:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:195:

```
Ser Asn Pro Arg Gly Arg Arg His Pro
 1               5
```

(2) INFORMATION FOR SEQ ID NO:196:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:196:

```
Thr Asn Ala Lys His Ser Ser His Asn
 1               5
```

(2) INFORMATION FOR SEQ ID NO:197:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:197:

```
Ser Ser His Asn Arg Arg Leu Arg Thr Arg
 1               5                   10
```

(2) INFORMATION FOR SEQ ID NO:198:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:198:

```
Arg Arg Leu Arg Thr Arg Ser Arg Pro Asn
 1               5                   10
```

(2) INFORMATION FOR SEQ ID NO:199:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:199:

```
Arg Val Gly Gln Cys Thr Asp Ser Asp Val Arg Arg Pro Trp Ala Arg
 1               5                   10                  15
Ser Cys Ala
```

(2) INFORMATION FOR SEQ ID NO:200:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:200:

```
Val Arg Arg Pro Trp Ala Arg Ser Cys Ala His Gln Gly Cys Gly Ala
 1               5                  10                  15
Gly Thr Arg Asn Ser
            20
```

(2) INFORMATION FOR SEQ ID NO:201:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:201:

```
Gly Thr Arg Asn Ser His Gly Cys Ile Thr Arg Pro Leu Arg Gln Ala
 1               5                  10                  15
Ser Gln His
```

(2) INFORMATION FOR SEQ ID NO:202:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:202:

```
Ser Thr Pro Pro Ser Arg Glu Ala Tyr Ser Arg Pro Tyr Ser Val Asp
 1               5                  10                  15
Ser Asp Ser Asp Thr Met Ala Lys His Ser Ser His Asn Arg Arg Leu
            20                  25                  30
Arg Thr Arg Ser Arg Pro Asn Gly
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:203:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:203:

```
Tyr Ser Lys Val
 1
```

(2) INFORMATION FOR SEQ ID NO:204:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:204:

Phe Pro His Leu
1

(2) INFORMATION FOR SEQ ID NO:205:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:205:

Tyr Arg Gly Val
1

(2) INFORMATION FOR SEQ ID NO:206:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:206:

Tyr Gln Thr Ile
1

(2) INFORMATION FOR SEQ ID NO:207:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:207:

Thr Glu Gln Phe
1

(2) INFORMATION FOR SEQ ID NO:208:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:208:

Thr Glu Val Met
1

(2) INFORMATION FOR SEQ ID NO:209:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:209:

Thr Ser Ala Phe
1

(2) INFORMATION FOR SEQ ID NO:210:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:210:

Tyr Thr Arg Phe
1

(2) INFORMATION FOR SEQ ID NO:211:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 717 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...714
(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:211:

```
ATG TCC CCT ATA CTA GGT TAT TGG AAA ATT AAG GGC CTT GTG CAA CCC      48
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15

ACT CGA CTT CTT TTG GAA TAT CTT GAA GAA AAA TAT GAA GAG CAT TTG      96
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30

TAT GAG CGC GAT GAA GGT GAT AAA TGG CGA AAC AAA AAG TTT GAA TTG     144
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45

GGT TTG GAG TTT CCC AAT CTT CCT TAT TAT ATT GAT GGT GAT GTT AAA     192
```

```
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
     50                  55                  60

TTA ACA CAG TCT ATG GCC ATC ATA CGT TAT ATA GCT GAC AAG CAC AAC      240
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80

ATG TTG GGT GGT TGT CCA AAA GAG CGT GCA GAG ATT TCA ATG CTT GAA      288
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95

GGA GCG GTT TTG GAT ATT AGA TAC GGT GTT TCG AGA ATT GCA TAT AGT      336
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110

AAA GAC TTT GAA ACT CTC AAA GTT GAT TTT CTT AGC AAG CTA CCT GAA      384
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125

ATG CTG AAA ATG TTC GAA GAT CGT TTA TGT CAT AAA ACA TAT TTA AAT      432
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140

GGT GAT CAT GTA ACC CAT CCT GAC TTC ATG TTG TAT GAC GCT CTT GAT      480
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160

GTT GTT TTA TAC ATG GAC CCA ATG TGC CTG GAT GCG TTC CCA AAA TTA      528
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175

GTT TGT TTT AAA AAA CGT ATT GAA GCT ATC CCA CAA ATT GAT AAG TAC      576
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190

TTG AAA TCC AGC AAG TAT ATA GCA TGG CCT TTG CAG GGC TGG CAA GCC      624
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205

ACG TTT GGT GGT GGC GAC CAT CCT CCA AAA TCG GAT CTG GTT CCG CGT      672
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220

GGA TCC CCA GGA ATT CCC GGG TCG ACT CGA GCG GCC GCA TCG TGA          717
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser
225                 230                 235
```

(2) INFORMATION FOR SEQ ID NO:212:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 238 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:212:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1               5                   10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
```

```
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser
225                 230                 235
```

(2) INFORMATION FOR SEQ ID NO:213:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 282 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:213:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1               5                   10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Gln
```

225 230 235 240
Gly Ser Lys Gln Cys Met Gln Tyr Arg Thr Gly Arg Leu Thr Val Gly
245 250 255
Ser Glu Tyr Gly Cys Gly Met Asn Pro Ala Arg His Ala Thr Pro Ala
260 265 270
Tyr Pro Ala Arg Leu Leu Pro Arg Tyr Arg
275 280

(2) INFORMATION FOR SEQ ID NO:214:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 282 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:214:

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1 5 10 15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
20 25 30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
35 40 45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
50 55 60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65 70 75 80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85 90 95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100 105 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115 120 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130 135 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145 150 155 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165 170 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180 185 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
195 200 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
210 215 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Asp
225 230 235 240
His Ala Leu Gly Thr Asn Leu Arg Ser Asp Asn Ala Lys Glu Pro Gly
245 250 255
Asp Tyr Asn Cys Cys Gly Asn Gly Asn Ser Thr Gly Arg Lys Val Phe
260 265 270
Asn Arg Arg Arg Pro Ser Ala Ile Pro Thr
275 280

(2) INFORMATION FOR SEQ ID NO:215:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 279 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:215:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Pro
225                 230                 235                 240
Cys Gly Gly Ser Trp Gly Arg Phe Met Gln Gly Gly Leu Phe Gly Gly
                245                 250                 255
Arg Thr Asp Gly Cys Gly Ala His Arg Asn Arg Thr Ser Ala Ser Leu
            260                 265                 270
Glu Pro Pro Ser Ser Asp Tyr
        275
```

(2) INFORMATION FOR SEQ ID NO:216:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 277 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:216:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
```

```
        115                     120                     125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                     135                     140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                     150                     155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                     170                     175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                     185                     190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                     200                     205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                     215                     220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Arg Gly
225                     230                     235                 240
Ser Thr Gly Thr Ala Gly Gly Glu Arg Ser Gly Val Leu Asn Leu His
                245                     250                     255
Thr Arg Asp Asn Ala Ser Gly Ser Gly Phe Lys Pro Trp Tyr Pro Ser
            260                     265                     270
Asn Arg Gly His Lys
        275
```

(2) INFORMATION FOR SEQ ID NO:217:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 277 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:217:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser His
225                 230                 235                 240
Ser Gly Gly Met Asn Arg Ala Tyr Gly Asp Val Phe Arg Glu Leu Arg
                245                 250                 255
```

```
Asp Arg Trp Asn Ala Thr Ser His His Thr Arg Pro Thr Pro Gln Leu
            260                 265                 270
Pro Arg Gly Pro Asn
        275
```

(2) INFORMATION FOR SEQ ID NO:218:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 248 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:218:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser His
225                 230                 235                 240
Ser Gly Gly Met Asn Arg Ala Tyr
                245
```

(2) INFORMATION FOR SEQ ID NO:219:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 248 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:219:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
```

Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
35 40 45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
50 55 60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65 70 75 80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85 90 95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100 105 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115 120 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130 135 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145 150 155 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165 170 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180 185 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
195 200 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
210 215 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Gly Asp
225 230 235 240
Val Phe Arg Glu Leu Arg Asp Arg
245

(2) INFORMATION FOR SEQ ID NO:220:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 248 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:220:

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1 5 10 15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
20 25 30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
35 40 45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
50 55 60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65 70 75 80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85 90 95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100 105 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115 120 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130 135 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145 150 155 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165 170 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180 185 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala

```
        195                     200                     205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                     215                     220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Trp Asn
225                     230                     235                     240
Ala Thr Ser His His Thr Arg Pro
                245
```

(2) INFORMATION FOR SEQ ID NO:221:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 247 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:221:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Thr Pro
225                 230                 235                 240
Gln Leu Pro Arg Gly Pro Asn
                245
```

(2) INFORMATION FOR SEQ ID NO:222:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 258 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:222:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
```

```
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Gly Asp
225                 230                 235                 240
Val Phe Arg Glu Leu Arg Asp Arg Trp Asn Ala Thr Ser His His Thr
                245                 250                 255
Arg Pro
```

(2) INFORMATION FOR SEQ ID NO:223:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 257 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:223:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
```

```
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Trp Asn
225                 230                 235                     240
Ala Thr Ser His His Thr Arg Pro Thr Pro Gln Leu Pro Arg Gly Pro
                245                 250                 255
Asn
```

(2) INFORMATION FOR SEQ ID NO:224:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 267 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:224:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Gly Asp
225                 230                 235                     240
Val Phe Arg Glu Leu Arg Asp Arg Trp Asn Ala Thr Ser His His Thr
                245                 250                 255
Arg Pro Thr Pro Gln Leu Pro Arg Gly Pro Asn
            260                 265
```

(2) INFORMATION FOR SEQ ID NO:225:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 277 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:225:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser His
225                 230                 235                 240
Ser Gly Gly Met Asn Arg Ala Tyr Gly Asp Val Phe Arg Glu Leu Arg
                245                 250                 255
Asp Arg Trp Asn Ala Thr Ser Ala Ala Thr Arg Pro Thr Pro Gln Leu
            260                 265                 270
Pro Arg Gly Pro Asn
        275
```

(2) INFORMATION FOR SEQ ID NO:226:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 277 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:226:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
```

```
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Ala
225                 230                 235                 240
Arg Asp Ser Gly Pro Ala Glu Asp Gly Ser Arg Ala Val Arg Leu Asn
                245                 250                 255
Gly Val Glu Asn Ala Asn Thr Arg Lys Ser Ser Arg Ser Asn Pro Arg
            260                 265                 270
Gly Arg Arg His Pro
        275
```

(2) INFORMATION FOR SEQ ID NO:227:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 257 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:227:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1               5                   10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
```

```
    195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Ala
225                 230                 235                 240
Arg Asp Ser Gly Pro Ala Glu Asp Gly Ser Arg Ala Val Arg Leu Asn
                245                 250                 255
Gly
```

(2) INFORMATION FOR SEQ ID NO:228:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 259 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:228:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Asp Gly
225                 230                 235                 240
Ser Arg Ala Val Arg Leu Asn Gly Val Glu Asn Ala Asn Thr Arg Lys
                245                 250                 255
Ser Ser Arg
```

(2) INFORMATION FOR SEQ ID NO:229:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 257 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:229:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Glu Asn
225                 230                 235                 240
Ala Asn Thr Arg Lys Ser Ser Arg Ser Asn Pro Arg Gly Arg Arg His
                245                 250                 255
Pro
```

(2) INFORMATION FOR SEQ ID NO:230:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 248 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:230:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
```

```
    130                     135                     140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                     150                     155                     160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                     170                     175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                     185                     190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                     200                     205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                     215                     220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Glu Asn
225                     230                     235                     240
Ala Asn Thr Arg Lys Ser Ser Arg
                245
```

(2) INFORMATION FOR SEQ ID NO:231:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 248 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:231:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Arg Lys
225                 230                 235                 240
Ser Ser Arg Ser Asn Pro Arg Gly
                245
```

(2) INFORMATION FOR SEQ ID NO:232:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 247 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:232:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Asn
225                 230                 235                 240
Pro Arg Gly Arg Arg His Pro
                245
```

(2) INFORMATION FOR SEQ ID NO:233:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 249 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:233:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
```

Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115 120 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130 135 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145 150 155 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165 170 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180 185 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
195 200 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
210 215 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Thr Arg
225 230 235 240
Lys Ser Ser Arg Ser Asn Pro Arg Gly
245

(2) INFORMATION FOR SEQ ID NO:234:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 277 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:234:

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1 5 10 15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
20 25 30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
35 40 45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
50 55 60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65 70 75 80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85 90 95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100 105 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115 120 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130 135 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145 150 155 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165 170 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180 185 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
195 200 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
210 215 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Thr
225 230 235 240
Pro Pro Ser Arg Glu Ala Tyr Ser Arg Pro Tyr Ser Val Asp Ser Asp
245 250 255
Ser Asp Thr Asn Ala Lys His Ser Ser His Asn Arg Arg Leu Arg Thr
260 265 270
Arg Ser Arg Pro Asn

275

(2) INFORMATION FOR SEQ ID NO:235:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 258 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:235:

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1 5 10 15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
20 25 30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
35 40 45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
50 55 60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65 70 75 80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85 90 95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100 105 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115 120 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130 135 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145 150 155 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165 170 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180 185 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
195 200 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
210 215 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Thr
225 230 235 240
Pro Pro Ser Arg Glu Ala Tyr Ser Arg Pro Tyr Ser Val Asp Ser Asp
245 250 255
Ser Asp

(2) INFORMATION FOR SEQ ID NO:236:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 259 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:236:

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1 5 10 15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
20 25 30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu

```
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Arg
225                 230                 235                 240
Pro Tyr Ser Val Asp Ser Asp Ser Asp Thr Asn Ala Lys His Ser Ser
                245                 250                 255
His Asn Arg
```

(2) INFORMATION FOR SEQ ID NO:237:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 257 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:237:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1               5                   10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
```

```
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Thr Asn
225                 230                 235                     240
Ala Lys His Ser Ser His Asn Arg Arg Leu Arg Thr Arg Ser Arg Pro
                245                 250                 255
Asn
```

(2) INFORMATION FOR SEQ ID NO:238:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 247 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:238:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1               5                   10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Thr Asn
225                 230                 235                     240
Ala Lys His Ser Ser His Asn
                245
```

(2) INFORMATION FOR SEQ ID NO:239:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 248 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:239:

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1 5 10 15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
20 25 30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
35 40 45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
50 55 60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65 70 75 80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85 90 95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100 105 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115 120 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130 135 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145 150 155 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165 170 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180 185 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
195 200 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
210 215 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Ser Ser
225 230 235 240
His Asn Arg Arg Leu Arg Thr Arg
245

(2) INFORMATION FOR SEQ ID NO:240:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 248 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:240:

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1 5 10 15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
20 25 30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
35 40 45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
50 55 60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65 70 75 80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85 90 95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100 105 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115 120 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130 135 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp

```
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Arg Arg
225                 230                 235                 240
Leu Arg Thr Arg Ser Arg Pro Asn
                245
```

(2) INFORMATION FOR SEQ ID NO:241:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 282 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:241:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Arg Val
225                 230                 235                 240
Gly Gln Cys Thr Asp Ser Asp Val Arg Arg Pro Trp Ala Arg Ser Cys
                245                 250                 255
Ala His Gln Gly Cys Gly Ala Gly Thr Arg Asn Ser His Gly Cys Ile
            260                 265                 270
Thr Arg Pro Leu Arg Gln Ala Ser Ala His
        275                 280
```

(2) INFORMATION FOR SEQ ID NO:242:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 257 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:242:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Arg Val
225                 230                 235                 240
Gly Gln Cys Thr Asp Ser Asp Val Arg Arg Pro Trp Ala Arg Ser Cys
                245                 250                 255

Ala
```

(2) INFORMATION FOR SEQ ID NO:243:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 259 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:243:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
```

```
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Val Arg
225                 230                 235                 240
Arg Pro Trp Ala Arg Ser Cys Ala His Gln Gly Cys Gly Ala Gly Thr
                245                 250                 255
Arg Asn Ser
```

(2) INFORMATION FOR SEQ ID NO:244:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 257 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:244:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1              5                   10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Gly Thr
```

```
225                 230                     235                     240
Arg Asn Ser His Gly Cys Ile Thr Arg Pro Leu Arg Gln Ala Ser Gln
                245                     250                     255
His
```

(2) INFORMATION FOR SEQ ID NO:245:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 282 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:245:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Arg Tyr
225                 230                 235                 240
Lys His Asp Ile Gly Cys Asp Ala Gly Val Asp Lys Lys Ser Ser Ser
                245                 250                 255
Val Arg Gly Gly Cys Gly Ala His Ser Ser Pro Pro Arg Ala Gly Arg
            260                 265                 270
Gly Pro Arg Gly Thr Met Val Ser Arg Leu
        275                 280
```

(2) INFORMATION FOR SEQ ID NO:246:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 262 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:246:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Arg Tyr
225                 230                 235                 240
Lys His Asp Ile Gly Cys Asp Ala Gly Val Asp Lys Lys Ser Ser Ser
                245                 250                 255
Val Arg Gly Gly Cys Gly
            260
```

(2) INFORMATION FOR SEQ ID NO:247:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 264 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:247:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
```

```
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Gly Cys
225                 230                 235                 240
Asp Ala Gly Val Asp Lys Lys Ser Ser Ser Val Arg Gly Gly Cys Gly
                245                 250                 255
Ala His Ser Ser Pro Pro Arg Ala
            260
```

(2) INFORMATION FOR SEQ ID NO:248:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 259 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:248:

```
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
 1               5                  10                  15
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
            20                  25                  30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
        35                  40                  45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
    50                  55                  60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65                  70                  75                  80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
                85                  90                  95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
            100                 105                 110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
        115                 120                 125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
    130                 135                 140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145                 150                 155                 160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
                165                 170                 175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
            180                 185                 190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
        195                 200                 205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
    210                 215                 220
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser Gly Ala
225                 230                 235                 240
His Ser Ser Pro Pro Arg Ala Gly Arg Gly Pro Arg Gly Thr Met Val
                245                 250                 255
Ser Arg Leu
```

(2) INFORMATION FOR SEQ ID NO:249:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:249:

```
Ser Gly Ser Pro Pro Cys Cys Cys Ser Trp Gly Arg Phe Met Gln Gly
 1               5                  10                  15
Gly Leu Phe Gly Gly Arg Thr Asp Gly Cys Gly Ala His Arg Asn Arg
            20                  25                  30
Thr Ser Ala Ser Leu Glu Pro Pro Ser Ser Asp Tyr
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:250:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:250:

```
Ser His Ser Gly Gly Met Asn Arg Ala Tyr Gly Asp Val Phe Arg Glu
 1               5                  10                  15
Leu Arg Asp Arg Trp Asn Ala Thr Ser His His Thr Arg Pro Thr Pro
            20                  25                  30
Gln Leu Pro Arg Gly Pro Asn Ser
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:251:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:251:

```
Asp Thr Asn Ala Lys His Ser Ser His Asn Arg Arg Leu Arg Thr Arg
 1               5                  10                  15
Ser Arg Pro Asn Gly
            20
```

(2) INFORMATION FOR SEQ ID NO:252:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:252:

```
Cys Gly Ala Gly Thr Arg Asn Ser His Gly Cys Ile Thr Arg Pro Leu
 1               5                  10                  15
```

Arg Gln Ala Ser Ala His Gly
20

(2) INFORMATION FOR SEQ ID NO:253:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Modified Site
(B) LOCATION: 1
(D) OTHER INFORMATION: "Xaa=Ser or Thr"

(A) NAME/KEY: Modified Site
(B) LOCATION: 3
(D) OTHER INFORMATION: "Xaa=Arg or Lys"

(A) NAME/KEY: Modified Site
(B) LOCATION: 4
(D) OTHER INFORMATION: "Xaa=Lys or Arg"

(A) NAME/KEY: Modified Site
(B) LOCATION: 6
(D) OTHER INFORMATION: "Xaa=Ser or Leu"

(A) NAME/KEY: Modified Site
(B) LOCATION: 7
(D) OTHER INFORMATION: "Xaa=Arg, Ile, Val or Ser"

(A) NAME/KEY: Modified Site
(B) LOCATION: 8
(D) OTHER INFORMATION: "Xaa=Ser, Tyr, Phe or His"

(A) NAME/KEY: Modified Site
(B) LOCATION: 10
(D) OTHER INFORMATION: "Xaa=Phe, His or Arg"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:253:

Xaa Thr Xaa Xaa Ser Xaa Xaa Xaa Asn Xaa Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:254:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Modified Site
(B) LOCATION: 2
(D) OTHER INFORMATION: "Xaa=Ser, Ala or Gly"

(A) NAME/KEY: Modified Site
(B) LOCATION: 4
(D) OTHER INFORMATION: "Xaa=Val or Gln"

(A) NAME/KEY: Modified Site
(B) LOCATION: 7
(D) OTHER INFORMATION: "Xaa=Pro, Gly or Ser"

(A) NAME/KEY: Modified Site
(B) LOCATION: 8
(D) OTHER INFORMATION: "Xaa=Trp or Tyr"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:254:

```
Asp Xaa Asp Xaa Arg Arg Xaa Xaa
 1               5
```

(2) INFORMATION FOR SEQ ID NO:255:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: Modified Site
(B) LOCATION: 7
(D) OTHER INFORMATION: "Xaa=Ala or Phe"

(A) NAME/KEY: Modified Site
(B) LOCATION: 8
(D) OTHER INFORMATION: "Xaa=Arg or His"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:255:

```
Val Arg Ser Gly Cys Gly Xaa Xaa Ser Ser
 1               5                   10
```

(2) INFORMATION FOR SEQ ID NO:256:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:256:

```
Asn Thr Arg Lys Ser Ser Arg Ser Asn Pro Arg
 1               5                   10
```

(2) INFORMATION FOR SEQ ID NO:257:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:257:

```
Ser Thr Lys Arg Ser Leu Ile Tyr Asn His Arg
```

1 5 10

(2) INFORMATION FOR SEQ ID NO:258:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:258:

Ser Thr Gly Arg Lys Val Phe Asn Arg Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:259:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:259:

Thr Asn Ala Lys His Ser Ser His Asn Arg Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO:260:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:260:

Asp Ser Asp Val Arg Arg Pro Trp
1 5

(2) INFORMATION FOR SEQ ID NO:261:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:261:

Ala Ala Asp Gln Arg Arg Gly Trp
1 5

(2) INFORMATION FOR SEQ ID NO:262:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:262:

```
Asp Gly Arg Gly Gly Arg Ser Tyr
 1               5
```

(2) INFORMATION FOR SEQ ID NO:263:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:263:

```
Arg Val Arg Ser
 1
```

(2) INFORMATION FOR SEQ ID NO:264:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:264:

```
Ser Val Arg Ser Gly Cys Gly Phe Arg Gly Ser Ser
 1               5                   10
```

(2) INFORMATION FOR SEQ ID NO:265:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:265:

```
Ser Val Arg Gly Gly Cys Gly Ala His Ser Ser
 1               5                   10
```

WHAT IS CLAIMED IS:

1. A purified protein which specifically binds to a gastro-intestinal tract receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI.

2. A protein which binds specifically to a gastro-intestinal transport receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, in which the protein comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1-55 or a binding portion thereof.

3. A protein which binds specifically to a gastro-intestinal transport receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, in which the amino acid sequence of the protein is selected from the group consisting of SEQ ID NOS:1-55, or a binding portion thereof.

4. The protein of claim 2 which comprises the amino acid sequence substantially as set forth in: SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 30, SEQ ID NO: 43, SEQ ID NO: 46, or SEQ ID NO: 52, or a binding portion thereof.

5. The protein of claim 3, the amino acid sequence of which consists of the amino acid sequence substantially as set forth in: SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 30, SEQ ID NO: 43, SEQ ID NO: 46, or SEQ ID NO: 52, or a binding portion thereof.

6. A protein of not more than 50 amino acids in length which specifically binds to a gastro-intestinal transport receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, in which the protein includes, positioned anywhere along its sequence, the contiguous amino

acid sequence of: Xaa_1 Thr Xaa_2 Xaa_3 Ser Xaa_4 Xaa_5 Xaa_6 Asn Xaa_7 Arg (SEQ ID NO:253), where Xaa_1 is Ser or Thr; Xaa_2 is Arg or Lys; Xaa_3 is Lys or Arg; Xaa_4 is Ser or Leu; Xaa_5 is Arg, Ile, Val, or Ser; Xaa_6 is Ser, Tyr, Phe, or His; and Xaa_7 is Pro, His or Arg.

7. The protein of claim 6 which is not more than 40 amino acids in length.

8. The protein of claim 6 which is not more than 30 amino acids in length.

9. The protein of claim 6 which is not more than 20 amino acids in length.

10. A protein of not more than 50 amino acids in length which specifically binds to a gastro-intestinal transport receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, in which the protein includes, positioned anywhere along its sequence, the contiguous amino acid sequence of: Asp Xaa_1 Asp Xaa_2 Arg Arg Xaa_3 Xaa_4 (SEQ ID NO:254) where Xaa_1 is Ser, Ala, or Gly; Xaa_2 is Val or Gln; Xaa_3 is Pro, Gly, or Ser; and Xaa_4 is Trp or Tyr.

11. The protein of claim 10 which is not more than 40 amino acids in length.

12. The protein of claim 10 which is not more than 30 amino acids in length.

13. The protein of claim 10 which is not more than 20 amino acids in length.

14. A protein of not more than 50 amino acids in length which specifically binds to a gastro-intestinal transport receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, in which the protein includes,

positioned anywhere along its sequence, the contiguous amino acid sequence of: Val Arg Ser Gly Cys Gly Xaa_1 Xaa_2 Ser Ser (SEQ ID NO:255), where Xaa_1 is Ala or Phe; and Xaa_2 is Arg or His.

15. The protein of claim 14 which is not more than 40 amino acids in length.

16. The protein of claim 14 which is not more than 30 amino acids in length.

17. The protein of claim 14 which is not more than 20 amino acids in length.

18. A protein of not more than 50 amino acids in length which specifically binds to a gastro-intestinal transport receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, in which the protein includes, positioned anywhere along its sequence, the contiguous amino acid sequence of: NTRKSSRSNPR (SEQ ID NO:256) or STKRSLIYNHR (SEQ ID NO:257) or STGRKVFNRR (SEQ ID NO:258) or TNAKHSSHNRR (SEQ ID NO:259).

19. A protein of not more than 50 amino acids in length which specifically binds to a gastro-intestinal transport receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, in which the protein includes, positioned anywhere along its sequence, the contiguous amino acid sequence of: DSDVRRPW (SEQ ID NO:260) or AADQRRGW (SEQ ID NO:261) or DGRGGRSY (SEQ ID NO:262).

20. A protein of not more than 50 amino acids in length which specifically binds to a gastro-intestinal transport receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, in which the protein includes, positioned anywhere along its sequence, the contiguous amino

acid sequence of: RVRS (SEQ ID NO:263) or SVRSGCGFRGSS (SEQ ID NO:264) or SVRGGCGAHSS (SEQ ID NO:265).

21. The protein of claim 1, 2, 3, 6, 10, 14, 18, 19, or 20 which is purified.

22. A composition comprising the protein of claim 1, 2, 3, 6, 10, 14, 18, 19, or 20, bound to a material comprising an active agent, said active agent being of value in the treatment of a mammalian disease or disorder.

23. The composition of claim 22 in which the active agent is a drug.

24. The composition of claim 22 in which the material is a particle containing the active agent.

25. The composition of claim 22 in which the material is a slow-release device containing the drug.

26. The composition of claim 22 in which the protein is covalently or noncovalently bound to the material.

27. A composition comprising a chimeric protein bound to a material comprising an active agent, in which the chimeric protein comprises a sequence selected from the group consisting of SEQ ID NOS:1-55 or a binding portion thereof fused via a covalent bond to an amino acid sequence of a second protein, in which the active agent is of value in the treatment of a mammalian disease or disorder.

28. A composition comprising the protein of claim 1, 2, 3, 6, 10, 14, 18, 19, or 20 covalently bound to a particle containing a drug.

29. A composition comprising the protein of claim 1, 2, 3, 6, 10, 14, 18, 19, or 20 covalently bound to a drug.

30. The composition of claim 22 which facilitates the transport of the active agent through human or animal gastro-intestinal tissue.

31. A method of delivering an active agent *in vivo* comprising administering to a subject a purified composition of claim 22.

32. A method of delivering a drug to a subject comprising administering to the subject a purified composition of claim 30.

33. A method of delivering a drug to a subject comprising administering to the subject a purified composition of claim 31.

34. The method according to claim 31 in which the administering is oral.

35. The method according to claim 31 in which the active agent is a drug.

36. The method according to claim 31 in which the subject is a human.

37. The method according to claim 35 in which the subject is a human.

38. The method according to claim 31 in which said composition facilitates the transport of the active agent through human or animal gastro-intestinal tissue.

39. The method according to claim 33 in which the administering is oral.

40. A pharmaceutical composition comprising the composition of claim 22 in a pharmaceutically acceptable carrier suitable for use in humans *in vivo*.

41. A chimeric protein comprising at least 6 contiguous amino acids of an amino acid sequence selected from the group consisting of SEQ ID NOS:1-55, that specifically bind to a gastro-intestinal tract receptor, fused via a covalent bond to an amino acid sequence of a second protein.

42. An antibody which is capable of immunospecifically binding the protein of claim 2, 3, 6, 10, 14, 18, 19 or 20.

43. A molecule comprising a fragment of the antibody of claim 42, which fragment is capable of immunospecifically binding said protein.

44. A purified derivative of the protein of claim 1 or 2, which displays one or more functional activities of said protein.

45. The derivative of claim 44 which is able to be bound by an antibody directed against said protein.

46. A fragment of the protein of claim 2 comprising a domain of said protein.

47. A fragment of the protein of claim 3 comprising a domain of said protein.

48. A nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS:110-163.

49. A nucleic acid comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS:55-109.

50. An isolated nucleic acid comprising a nucleotide sequence encoding the protein of claim 1.

51. A nucleic acid comprising a nucleotide sequence encoding the protein of claim 2, 3, 6, 10, 14, 18, 19 or 20.

52. The nucleic acid of claim 51 which is a DNA.

53. The nucleic acid of claim 48 or 49 which is isolated.

54. The nucleic acid of claim 51 which is isolated.

55. An isolated nucleic acid comprising a nucleotide sequence complementary to the nucleotide sequence of claim 57.

56. An isolated nucleic acid comprising a nucleotide sequence encoding a fragment of the protein of claim 1, 2, or 3, which fragments bind to said gastro-intestinal tract receptor.

57. A nucleic acid comprising a nucleotide sequence encoding the chimeric protein of claim 41.

58. A nucleic acid comprising a nucleotide sequence encoding the fragment of claim 47.

59. The nucleic acid of claim 57 which is isolated.

60. The nucleic acid of claim 58 which is isolated.

61. A recombinant cell containing the nucleic acid of claim 48, 49 or 50.

62. A recombinant cell containing the nucleic acid of claim 51.

63. A recombinant cell containing the nucleic acid of claim 57.

64. A method of producing a protein comprising growing a recombinant cell containing the nucleic acid of claim 48, 49 or 50 such that the encoded protein is expressed by the cell, and recovering the expressed protein.

65. A method of producing a protein comprising growing a recombinant cell containing the nucleic acid of claim 51 such that the encoded protein is expressed by the cell, and recovering the expressed protein.

66. A method of producing a protein comprising growing a recombinant cell containing the nucleic acid of claim 57 such that the encoded protein is expressed by the cell, and recovering the expressed protein.

67. The product of the process of claim 64.

68. The product of the process of claim 65.

69. The product of the process of claim 66.

70. A pharmaceutical composition comprising a therapeutically effective amount of a composition comprising the protein of claim 1, 2, 3, 6, 10, 14, 18, 19, or 20; and a pharmaceutically acceptable carrier.

71. The chimeric protein of claim 41 in which said second protein is a drug.

72. A nucleic acid comprising a nucleotide sequence encoding the protein of claim 71.

73. A pharmaceutical composition comprising a therapeutically effective amount of the protein of claim 71, and a pharmaceutically acceptable carrier.

74. A pharmaceutical composition comprising a therapeutically effective amount of the nucleic acid of claim 78.

75. A method of delivering a drug to a subject comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of claim 80.

76. A method of treating or preventing a disease or disorder comprising administering to a subject in which such treatment or prevention is desired a therapeutically effective amount of the composition of claim 23.

77. A method of treating or preventing a disease or disorder comprising administering to a subject in which such treatment or prevention is desired a therapeutically effective amount of the composition of claim 28.

78. A method of treating or preventing a disease or disorder comprising administering to a subject in which such treatment or prevention is desired a therapeutically effective amount of the composition of claim 29.

79. The method according to claim 76 in which the disease or disorder is selected from the group consisting of:

hypertension, diabetes, osteoporosis, hemophilia, anemia, cancer, migraines, and angina pectoris.

80. The method according to claim 76 in which the subject is a human.

81. A composition comprising the protein of claim 1, 2, 3, 6, 10, 14, 18, 19, 20, or 46 wherein the protein is coated onto or absorbed onto or covalently bonded to the surface of a nano- or microparticle.

82. A nano- or microparticle formed from the protein of claim 1, 2, 3, 6, 10, 14, 18, 19, 20, or 46.

83. The composition of claim 87, wherein the nano- or microparticle is a drug-loaded or drug-encapsulating nano- or microparticle.

84. A method of detecting or measuring the level of a gastro-intestinal tract receptor in a sample, comprising contacting a sample suspected of containing a gastro-intestinal tract receptor with the protein of claim 1, 2, 3, 6, 10, 14, 18, 19, 20, or 46 under conditions conducive to binding between the protein and any of said receptor in said sample, and detecting or measuring any of said binding that occurs, in which the detected or measured amount of binding indicates the presence or amount of the receptor in the sample.

85. A method of identifying a molecule that specifically binds to a ligand selected from the group consisting of the protein of claim 1, 2, 3, 6, 10, 14, 18, or 19, a fragment of said protein comprising a domain of the protein, and a nucleic acid encoding said protein or fragment, comprising

(a) contacting said ligand with a plurality of molecules under conditions conducive to binding between said ligand and the molecules; and

(b) identifying a molecule within said plurality that specifically binds to said ligand.

86. An isolated nucleic acid encoding a fragment of a gastro-intestinal tract receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, or encoding a chimeric protein comprising said fragment, said fragment consisting essentially of the extracellular domain of the receptor.

87. A cell containing and capable of expressing a recombinant nucleic acid encoding a fragment of a gastro-intestinal tract receptor selected from the group consisting of HPT1, hPEPT1, D2H, and hSI, or encoding a chimeric protein comprising said fragment, said fragment consisting essentially of the extracellular domain of the receptor.

88. The cell of claim 87 which contains an expression vector comprising a nucleotide sequence encoding said fragment operably linked to a heterologous promoter.

89. A method for identifying a molecule that specifically binds to a gastro-intestinal tract receptor comprising contacting a fragment of the receptor, or a chimeric protein comprising said fragment, with a plurality of test molecules under conditions conducive to binding between said fragment or protein and the molecules, and identifying a molecule within said plurality that specifically binds to said fragment or protein, in which the fragments consist essentially of the extracellular domain of the receptor.

90. The composition of claim 22 for use as a medicament.

91. The composition of claim 28 for use as a medicament.

92. The composition of claim 29 for use as a medicament.

93. The composition of claim 81 for use as a medicament.

94. The composition of claim 23 in which the drug is insulin or leuprolide.

95. The composition of claim 24 in which the active agent is insulin or leuprolide.

96. The composition of claim 25 in which the drug is insulin or leuprolide.

97. The composition of claim 28 in which the drug is insulin or leuprolide.

```
                  20                   40                   60
MGMSKSHSFFGYPLSIFFIV VNEFCERFSYYGMRAILILY FTNFISWDDNLSTAIYHTFV

                  80                  100                  120
ALCYLTPILGALIADSWLGK FKTIVSLSIVYTIGQAVTSV SSINDLTDHNHDGTPDSLPV

                 140                  160                  180
HVVLSLIGLALIALGTGGIK PCVSAFGGDQFEEGQEKQRN RFFSIFYLAINAGSLLSTII

                 200                  220                  240
TPMLRVQQCGIHSKQACYPL AFGVPAALMAVALIVFVLGS GMYKKFKPQGNIMGKVAKCI

                 260                  280                  300
GFAIKNRFRHRSKAFPKREH WLDWAKEKYDERLISQIKMV TRVMFLYIPLPMFWALFDQQ

                 320                  340                  360
GSRWTLQATTMSGKIGALEI QPDQMQTVNAILIVIMVPIF DAVLYPLIAKCGFNFTSLKK

                 380                  400                  420
MAVGMVLASMAFVVAAIVQV EIDKTLPVFPKGNEVQIKVL NIGNNTMNISLPGEMVTLGP

                 440                  460                  480
MSQTNAFMTFDVNKLTRINI SSPGSPVTAVTDDFKQGQRH TLLVWAPNHYQVVKDGLNQK

                 500                  520                  540
PEKGENGIRFVNTFNELITI TMSGKVYANISSYNASTYQF FPSGIKGFTISSTEIPPQCQ

                 560                  580                  600
PNFNTFYLEFGSAYTYIVQR KNDSCPEVKVFEDISANTVN MALQIPQYFLLTCGEVVFSV

                 620                  640                  660
TGLEFSYSQAPSNMKSVLQA GWLLTVAVGNIIVLIVAGAG QFSKQWAEYILFAALLLVVC

                 680                  700      708
VIFAIMARFYTYINPAEIEA QFDEDEKKNRLEKSNPYFMS GANSQKQM
```

FIG.1

```
   1 gaattccgtc tcgaccactg aatggaagaa aaggactttt aaccaccatt ttgtgactta
  61 cagaaaggaa tttgaataaa gaaaactatg atacttcagg cccatcttca ctccctgtgt
                                       M  I  L  Q  A  H  L  H  S  L  C
 121 cttcttatgc tttatttggc aactggatat ggccaagagg ggaagtttag tggacccctg
      L  L  M  L  Y  L  A  T  G  Y  G  Q  E  G  K  F  S  G  P  L
 181 aaacccatga cattttctat ttatgaaggc caagaaccga gtcaaattat attccagttt
      K  P  M  T  F  S  I  Y  E  G  Q  E  P  S  Q  I  I  F  Q  F
 241 aaggccaatc ctcctgctgt gacttttgaa ctaactgggg agacagacaa catatttgtg
      K  A  N  P  P  A  V  T  F  E  L  T  G  E  T  D  N  I  F  V
 301 atagaacggg agggacttct gtattacaac agagccttgg acagggaaac aagatctact
      I  E  R  E  G  L  L  Y  Y  N  R  A  L  D  R  E  T  R  S  T
 361 cacaatctcc aggttgcagc cctggacgct aatggaatta tagtggaggg tccagtccct
      H  N  L  Q  V  A  A  L  D  A  N  G  I  I  V  E  G  P  V  P
 421 atcaccatag aagtgaagga catcaacgac aatcgaccca cgtttctcca gtcaaagtac
      I  T  I  E  V  K  D  I  N  D  N  R  P  T  F  L  Q  S  K  Y
 481 gaaggctcag taaggcagaa ctctcgccca ggaaagccct tcttgtatgt caatgccaca
      E  G  S  V  R  Q  N  S  R  P  G  K  P  F  L  Y  V  N  A  T
 541 gacctggatg atccggccac tcccaatggc cagctttatt accagattgt catccagctt
      D  L  D  D  P  A  T  P  N  G  Q  L  Y  Y  Q  I  V  I  Q  L
 601 cccatgatca acaatgtcat gtactttcag atcaacaaca aaacgggagc catctctctt
      P  M  I  N  N  V  M  Y  F  Q  I  N  N  K  T  G  A  I  S  L
 661 acccgagagg gatctcagga attgaatcct gctaagaatc cttcctataa tctggtgatc
      T  R  E  G  S  Q  E  L  N  P  A  K  N  P  S  Y  N  L  V  I
 721 tcagtgaagg acatgggagg ccagagtgag aattccttca gtgataccac atctgtggat
      S  V  K  D  M  G  G  Q  S  E  N  S  F  S  D  T  T  S  V  D
 781 atcatagtga cagagaatat ttggaaagca ccaaaacctg tggagatggt ggaaaactca
      I  I  V  T  E  N  I  W  K  A  P  K  P  V  E  M  V  E  N  S
 841 actgatcctc accccatcaa aatcactcag gtgcggtgga atgatcccgg tgcacaatat
      T  D  P  H  P  I  K  I  T  Q  V  R  W  N  D  P  G  A  Q  Y
 901 tccttagttg acaaagagaa gctgccaaga ttcccatttt caattgacca ggaaggagat
      S  L  V  D  K  E  K  L  P  R  F  P  F  S  I  D  Q  E  G  D
 961 atttacgtga ctcagccctt ggaccgagaa gaaaaggatg catatgtttt ttatgcagtt
      I  Y  V  T  Q  P  L  D  R  E  E  K  D  A  Y  V  F  Y  A  V
1021 gcaaaggatg agtacggaaa accactttca tatccgctgg aaattcatgt aaaagttaaa
      A  K  D  E  Y  G  K  P  L  S  Y  P  L  E  I  H  V  K  V  K
1081 gatattaatg ataatccacc tacatgtccg tcaccagtaa ccgtatttga ggtccaggag
      D  I  N  D  N  P  P  T  C  P  S  P  V  T  V  F  E  V  Q  E
1141 aatgaacgac tgggtaacag tatcgggacc cttactgcac atgacaggga tgaagaaaat
      N  E  R  L  G  N  S  I  G  T  L  T  A  H  D  R  D  E  E  N
1201 actgccaaca gttttctaaa ctacaggatt gtggagcaaa ctcccaaact tcccatggat
      T  A  N  S  F  L  N  Y  R  I  V  E  Q  T  P  K  L  P  M  D
```

FIG.2A

```
1261 ggactcttcc taatccaaac ctatgctgga atgttacagt tagctaaaca gtccttgaag
       G  L  F   L  I  Q   T  Y  A  G   M  L  Q   L  A  K   Q  S  L  K
1321 aagcaagata ctcctcagta caacttaacg atagaggtgt ctgacaaaga tttcaagacc
       K  Q  D   T  P  Q   Y  N  L  T   I  E  V   S  D  K   D  F  K  T
1381 ctttgttttg tgcaaatcaa cgttattgat atcaatgatc agatccccat ctttgaaaaa
       L  C  F   V  Q  I   N  V  I  D   I  N  D   Q  I  P   I  F  E  K
1441 tcagattatg gaaacctgac tcttgctgaa gacacaaaca ttgggtccac catcttaacc
       S  D  Y   G  N  L   T  L  A  E   D  T  N   I  G  S   T  I  L  T
1501 atccaggcca ctgatgctga tgagccattt actgggagtt ctaaaattct gtatcatatc
       I  Q  A   T  D  A   D  E  P  F   T  G  S   S  K  I   L  Y  H  I
1561 ataaagggag acagtgaggg acgcctgggg gttgacacag atccccatac caacaccgga
       I  K  G   D  S  E   G  R  L  G   V  D  T   D  P  H   T  N  T  G
1621 tatgtcataa ttaaaaagcc tcttgatttt gaaacagcag ctgtttccaa cattgtgttc
       Y  V  I   I  K  K   P  L  D  F   E  T  A   A  V  S   N  I  V  F
1681 aaagcagaaa atcctgagcc tctagtgttt ggtgtgaagt acaatgcaag ttcttttgcc
       K  A  E   N  P  E   P  L  V  F   G  V  K   Y  N  A   S  S  F  A
1741 aagttcacgc ttattgtgac agatgtgaat gaagcacctc aattttccca acacgtattc
       K  F  T   L  I  V   T  D  V  N   E  A  P   Q  F  S   Q  H  V  F
1801 caagcgaaag tcagtgagga tgtagctata ggcactaaag tgggcaatgt gactgccaag
       Q  A  K   V  S  E   D  V  A  I   G  T  K   V  G  N   V  T  A  K
1861 gatccagaag gtctggacat aagctattca ctgaggggag acacaagagg ttggcttaaa
       D  P  E   G  L  D   I  S  Y  S   L  R  G   D  T  R   G  W  L  K
1921 attgaccacg tgactggtga gatctttagt gtggctccat tggacagaga agccggaagt
       I  D  H   V  T  G   E  I  F  S   V  A  P   L  D  R   E  A  G  S
1981 ccatatcggg tacaagtggt ggccacagaa gtaggggggt cttccttaag ctctgtgtca
       P  Y  R   V  Q  V   V  A  T  E   V  G  G   S  S  L   S  S  V  S
2041 gagttccacc tgatccttat ggatgtgaat gacaaccctc ccaggctagc caaggactac
       E  F  H   L  I  L   M  D  V  N   D  N  P   P  R  L   A  K  D  Y
2101 acgggcttgt tcttctgcca tcccctcagt gcacctggaa gtctcatttt cgaggctact
       T  G  L   F  F  C   H  P  L  S   A  P  G   S  L  I   F  E  A  T
2161 gatgatgatc agcacttatt tcggggtccc cattttacat ttccctcgg cagtggaagc
       D  D  D   Q  H  L   F  R  G  P   H  F  T   F  S  L   G  S  G  S
2221 ttacaaaacg actgggaagt ttccaaaatc aatggtactc atgcccgact gtctaccagg
       L  Q  N   D  W  E   V  S  K  I   N  G  T   H  A  R   L  S  T  R
2281 cacacagact ttgaggagag ggcgtatgtc gtcttgatcc gcatcaatga tgggggtcgg
       H  T  D   F  E  E   R  A  Y  V   V  L  I   R  I  N   D  G  G  R
2341 ccacccttgg aaggcattgt ttctttacca gttacattct gcagttgtgt ggaaggaagt
       P  P  L   E  G  I   V  S  L  P   V  T  F   C  S  C   V  E  G  S
2401 tgtttccggc cagcaggtca ccagactggg atacccactg tgggcatggc agttggtata
       C  F  R   P  A  G   H  Q  T  G   I  P  T   V  G  M   A  V  G  I
```

FIG.2B

```
2461 ctgctgacca cccttctggt gattggtata attttagcag ttgtgtttat ccgcataaag
      L  L  T   T  L  L   V  I  G   I   I  L  A   V  V  F   I  R  I  K
2521 aaggataaag gcaaagataa tgttgaaagt gctcaagcat ctgaagtcaa acctctgaga
      K  D  K   G  K  D   N  V  E  S   A  Q  A   S  E  V   K  P  L  R
2581 agctgaattt gaaaaggaat gtttgcattt atatagcaag tgctatttca gcaacaacca
      S

2641 tctcatccta ttacttttca tctaacgtgc attataattt tttaaacaga tattccctct
2701 tgtcctttaa tatttgctaa atatttcttt tttgaggtgg agtcttgctc tgtcgcccag
2761 gctggagtac agtggtgtga tcccagctca ctgcaacctc cgcctcctgg gttcacatga
2821 ttctcctgcc tcagcttcct aagtagctgg gtttacaggc acccaccacc atgcccagct
2881 aatttttgta tttttaatag agacggggtt tcgccatttg gccaggatgg tcttgcactc
2941 ctgacgtcaa gtgatctgcc tgccttggtc tcccaataca ggcatgaacc actgcaccca
3001 cctacttaga tatttcatgt gctatagaca ttagagagat ttttcatttt tccatgacat
3061 ttttcctctc tgcaaatggc ttagctactt gtgtttttcc cttttggggc aagacagact
3121 cattaaatat tctgtacatt ttttctttat caaggagata tatcagtgtt gtctcataga
3181 actgcctgga ttccatttat gtttttttctg attccatcct gtgtcccctt catccttgac
3241 tcctttggta tttcactgaa tttcaaacat ttgtcagaga agaaaaaagt gaggactcag
3301 gaaaaataaa taaataaaag aacagccttt tgcggccgcg aattc
```

FIG.2C

20	40	60
MARKKFSGLEISLIVLFVIV	TIIAIALIVVLATKTPAVDE	ISDSTSTPATTRVTTNPSDS
80	100	120
GKCPNVLNDPVNVRINCIPE	QFPTEGICAQRGCCWRPWND	SLIPWCFFVDNHGYNVQDMT
140	160	180
TTSIGVEAKLNRIPSPTLFG	NDINSVLFTTQNQTPNRFRF	KITDPNNRRYEVPHQYVKEF
200	220	240
TGPTVSDTLYDVKVAQNPFS	IQVIRKSNGKTLFDTSIGPL	VYSDQYLQISARLPSDYIYG
260	280	300
IGEQVHKRFRHDLSWKTWPI	FTRDQLPGDNNNNLYGHQTF	FMCIEDTSGKSFGVFLMNSN
320	340	360
AMEIFIQPTPIVTYRVTGGI	LDFYILLGDTPEQVVQQYQQ	LVGLPAMPAYWNLGFQLSRW
380	400	420
NYKSLDVVKEVVRRNREAGI	PFDTQVTDIDYMEDKKDFTY	DQVAFNGLPQFVQDLHDHGQ
440	460	480
KYVIILDPAISIGRRANGTT	YATYERGNTQHVWINESDGS	TPIIGEVWPGLTVYPDFTNP
500	520	540
NCIDWWANECSIFHQEVQYD	GLWIDMNEVSSFIQGSTKGC	NVNKLNYPPFTPDILDKLMY
560	580	600
SKTICMDAVQNWGKQYDVHS	LYGYSMAIATEQAVQKVFPN	KRSFILTRSTFAGSGRHAAH
620	640	660
WLGDNTASWEQMEWSITGML	EFSLFGIPLVGADICGFVAE	TTEELCRRWMQLGAFYPFSR
680	700	720
NHNSDGYEHQDPAFFGQNSL	LVKSSRQYLTIRYTLLPFLY	TLFYKAHVFGETVARPVLHE
740	760	780
FYEDTNSWIEDTEFLWGPAL	LITPVLKQGADTVSAYIPDA	IWYDYESGAKRPWRKQRVDM
800	820	840
YLPADKIGLHLRGGYIIPIQ	EPDVTTTASRKNPLGLIVAL	GENNTAKGDFFWDDGETKDT
860	880	900
IQNGNYILYTFSVSNNTLDI	VCTHSSYQEGTTLAFQTVKI	LGLTDSVTEVRVAENNQPMN
920	940	960
AHSNFTYDASNQVLLIADLK	LNLGRNFSVQWNQIFSENER	FNCYPDADLATEQKCTQRGC
980	1000	1020
VWRTGSSLSKAPECYFPRQD	NSYSVNSARYSSMGITADLQ	LNTANARIKLPSDPISTLRV
1040	1060	1080
EVKYHKNDMLQFKIYDPQKK	RYEVPVPLNIPTTPISTYED	RLYDVEIKENPFGIQIRRRS
1100	1120	1140
SGRVIWDSWLPGFAFNDQFI	QISTRLPSEYIYGFGEVEHT	AFKRDLNWNTWGMFTRDQPP
1160	1180	1200
GYKLNSYGFHPYYMALEEEG	NAHGVFLLNSNAMDVTFQPT	PALTYRTVGGILDFYMFLGP
1220	1240	1260
TPQVATKQYHEVIGHPVMPA	YWALGFQLCRYGYANTSEVR	ELYDAMVAANIPYDVQYTDI

FIG.3A

```
                1280                 1300                 1320
DYMERQLDFTIGEAFQDLPQ FVDKIRGEGMRYIIILDPAI SGNETKTYPAFERGQQNDVF
                1340                 1360                 1380
VKWPNTNDICWAKVWPDLPN ITIDKTLTEDEAVNASRAHV AFPDFFRTSTAEWWAREIVD
                1400                 1420                 1440
FYNEKMKFDGLWIDMNEPSS FVNGTTTNQCRNDELNYPPY FPELTKRTDGLHFRTICMEA
                1460                 1480                 1500
EQILSDGTSVLHYDVHNLYG WSQMKPTHDALQKTTGKRGI VISRSTYPTSGRWGGHWLGD
                1520                 1540                 1560
NYARWDNMDKSIIGMMEFSL FGISYTGADICGFFNNSEYH LCTRWMQLGAFYPYSRNHNI
                1580                 1600                 1620
ANTRRQDPASWNETFAEMSR NILNIRYTLLPYFYTQMHEI HANGGTVIRPLLHEFFDEKP
                1640                 1660                 1680
TWDIFKQFLWGPAFMVTPVL EPYVQTVNAYVPNARWFDYH TGKDIGVRGQFQTFNASYDT
                1700                 1720                 1740
INLHVRGGHILPCQEPAQNT FYSRQKHMKLIVAADDNQMA QGSLFWDDGESIDTYERDLY
                1760                 1780                 1800
LSVQFNLNQTTLTSTILKRG YINKSETRLGSLHVWGKGTT PVNAVTLTYNGNKNSLPFNE
                1820     1827
DTTNMILRIDLTTHNVTLEE PIEINWS
```

FIG.3B

```
  1 gccttactgc aggaaggcac tccgaagaca taagtcggtg agacatggct gaagataaaa
                                                        M  A   E  D  K
 61 gcaagagaga ctccatcgag atgagtatga agggatgcca gacaaacaac gggtttgtcc
     S  K  R   D  S  I  E   M  S  M   K  G  C   Q  T  N  N   G  F  V
121 ataatgaaga cattctggag cagaccccgg atccaggcag ctcaacagac aacctgaagc
     H  N  E   D  I  L  E   Q  T  P   D  P  G   S  S  T  D   N  L  K
181 acagcaccag gggcatcctt ggctcccagg agcccgactt caagggcgtc cagccctatg
     H  S  T   R  G  I  L   G  S  Q   E  P  D   F  K  G  V   Q  P  Y
241 cggggatgcc caaggaggtg ctgttccagt tctctggcca ggcccgctac cgcatacctc
     A  G  M   P  K  E  V   L  F  Q   F  S  G   Q  A  R  Y   R  I  P
301 gggagatcct cttctggctc acagtggctt ctgtgctggt gctcatcgcg gccaccatag
     R  E  I   L  F  W  L   T  V  A   S  V  L   V  L  I  A   A  T  I
361 ccatcattgc cctctctcca aagtgcctag actggtggca ggaggggccc atgtaccaga
     A  I  I   A  L  S  P   K  C  L   D  W  W   Q  E  G  P   M  Y  Q
421 tctacccaag gtctttcaag gacagtaaca aggatgggaa cggagatctg aaaggtattc
     I  Y  P   R  S  F  K   D  S  N   K  D  G   N  G  D  L   K  G  I
481 aagataaact ggactacatc acagctttaa atataaaaac tgtttggatt acttcatttt
     Q  D  K   L  D  Y  I   T  A  L   N  I  K   T  V  W  I   T  S  F
541 ataaatcgtc ccttaaagat ttcagatatg gtgttgaaga tttccgggaa gttgatccca
     Y  K  S   S  L  K  D   F  R  Y   G  V  E   D  F  R  E   V  D  P
601 tttttggaac gatggaagat tttgagaatc tggttgcagc catacatgat aaaggtttaa
     I  F  G   T  M  E  D   F  E  N   L  V  A   A  I  H  D   K  G  L
661 aattaatcat cgatttcata ccaaaccaca cgagtgataa acatatttgg tttcaattga
     K  L  I   I  D  F  I   P  N  H   T  S  D   K  H  I  W   F  Q  L
721 gtcggacacg gacaggaaaa tatactgatt attatatctg gcatgactgt acccatgaaa
     S  R  T   R  T  G  K   Y  T  D   Y  Y  I   W  H  D  C   T  H  E
781 atggcaaaac cattccaccc aacaactggt taagtgtgta tggaaactcc agttggcact
     N  G  K   T  I  P  P   N  N  W   L  S  V   Y  G  N  S   S  W  H
841 ttgacgaagt gcgaaaccaa tgttattttc atcagtttat gaaagagcaa cctgatttaa
     F  D  E   V  R  N  Q   C  Y  F   H  Q  F   M  K  E  Q   P  D  L
901 atttccgcaa tcctgatgtt caagaagaaa taaaagaaat tttacggttc tggctcacaa
     N  F  R   N  P  D  V   Q  E  E   I  K  E   I  L  R  F   W  L  T
961 agggtgttga tggttttagt ttggatgctg ttaaattcct cctagaagca aagcacctga
     K  G  V   D  G  F  S   L  D  A   V  K  F   L  L  E  A   K  H  L
```

FIG.4A

```
1021 gagatgagat ccaagtaaat aagacccaaa tcccggacac ggtcacacaa tactcggagc
      R  D  E   I  Q  V  N   K  T  Q   I  P  D   T  V  T  Q   Y  S  E
1081 tgtaccatga cttcaccacc acgcaggtgg gaatgcacga cattgtccgc agcttccggc
      L  Y  H   D  F  T  T   T  Q  V   G  M  H   D  I  V  R   S  F  R
1141 agaccatgga ccaatacagc acggagcccg gcagatacag gttcatgggg actgaagcct
      Q  T  M   D  Q  Y  S   T  E  P   G  R  Y   R  F  M  G   T  E  A
1201 atgcagagag tattgacagg accgtgatgt actatggatt gccatttatc caagaagctg
      Y  A  E   S  I  D  R   T  V  M   Y  Y  G   L  P  F  I   Q  E  A
1261 attttccatt caacaattac ctcagcatgc tagacactgt ttctgggaac agcgtgtatg
      D  F  P   F  N  N  Y   L  S  M   L  D  T   V  S  G  N   S  V  Y
1321 aggttatcac atcctggatg gaaaacatgc cagaaggaaa atggcctaac tggatgattg
      E  V  I   T  S  W  M   E  N  M   P  E  G   K  W  P  N   W  M  I
1381 gtggaccaga cagttcacgg ctgacttcgc gtttggggaa tcagtatgtc aacgtgatga
      G  G  P   D  S  S  R   L  T  S   R  L  G   N  Q  Y  V   N  V  M
1441 acatgcttct tttcacactc cctggaactc ctataactta ctatggagaa gaaattggaa
      N  M  L   L  F  T  L   P  G  T   P  I  T   Y  Y  G  E   E  I  G
1501 tgggaaatat tgtagccgca aatctcaatg aaagctatga tattastacc cttcgctcaa
      M  G  N   I  V  A  A   N  L  N   E  S  Y   D  I  N  T   L  R  S
1561 agtcaccaat gcagtgggac aatagttcaa atgctggttt ttctgaagct agtaacacct
      K  S  P   M  Q  W  D   N  S  S   N  A  G   F  S  E  A   S  N  T
1621 ggttacctac caattcagat taccacactg tgaatgttga tgtccaaaag actcagccca
      W  L  P   T  N  S  D   Y  H  T   V  N  V   D  V  Q  K   T  Q  P
1681 gatcggcttt gaagttatat caagatttaa gtctacttca tgccaatgag ctactcctca
      R  S  A   L  K  L  Y   Q  D  L   S  L  L   H  A  N  E   L  L  L
1741 acaggggctg gttttgccat ttgaggaatg acagccacta tgttgtgtac acaagagagc
      N  R  G   W  F  C  H   L  R  N   D  S  H   Y  V  V  Y   T  R  E
1801 tggatggcat cgacagaatc tttatcgtgg ttctgaattt tggagaatca acactgttaa
      L  D  G   I  D  R  I   F  I  V   V  L  N   F  G  E  S   T  L  L
1861 atctacataa tatgatttcg ggccttcccg ctaaaataag aataaggtta agtaccaatt
      N  L  H   N  M  I  S   G  L  P   A  K  I   R  I  R  L   S  T  N
1921 ctgccgacaa aggcagtaaa gttgatacaa gtggcatttt tctggacaag ggagagggac
      S  A  D   K  G  S  K   V  D  T   S  G  I   F  L  D  K   G  E  G
1981 tcatctttga acacaacacg aagaatctcc ttcatcgcca aacagctttc agagatagat
      L  I  F   E  H  N  T   K  N  L   L  H  R   Q  T  A  F   R  D  R
2041 gctttgtttc caatcgagca tgctattcca gtgtactgaa catactgtat acctcgtgtt
      C  F  V   S  N  R  A   C  Y  S   S  V  L   N  I  L  Y   T  S  C
2101 aggcaccttt atgaagagat gaagacactg gcatttcagt gggattgtaa gcatttgtaa
2161 tagcttcatg tacagcatgc tgcttggtga acaatcatta attcttcgat atttctgtag
2221 cttgaatgta accgctttaa gaaaggttct caaatgtttt gaaaaaaata aaatgtttaa
2281 aagt
```

FIG.4B

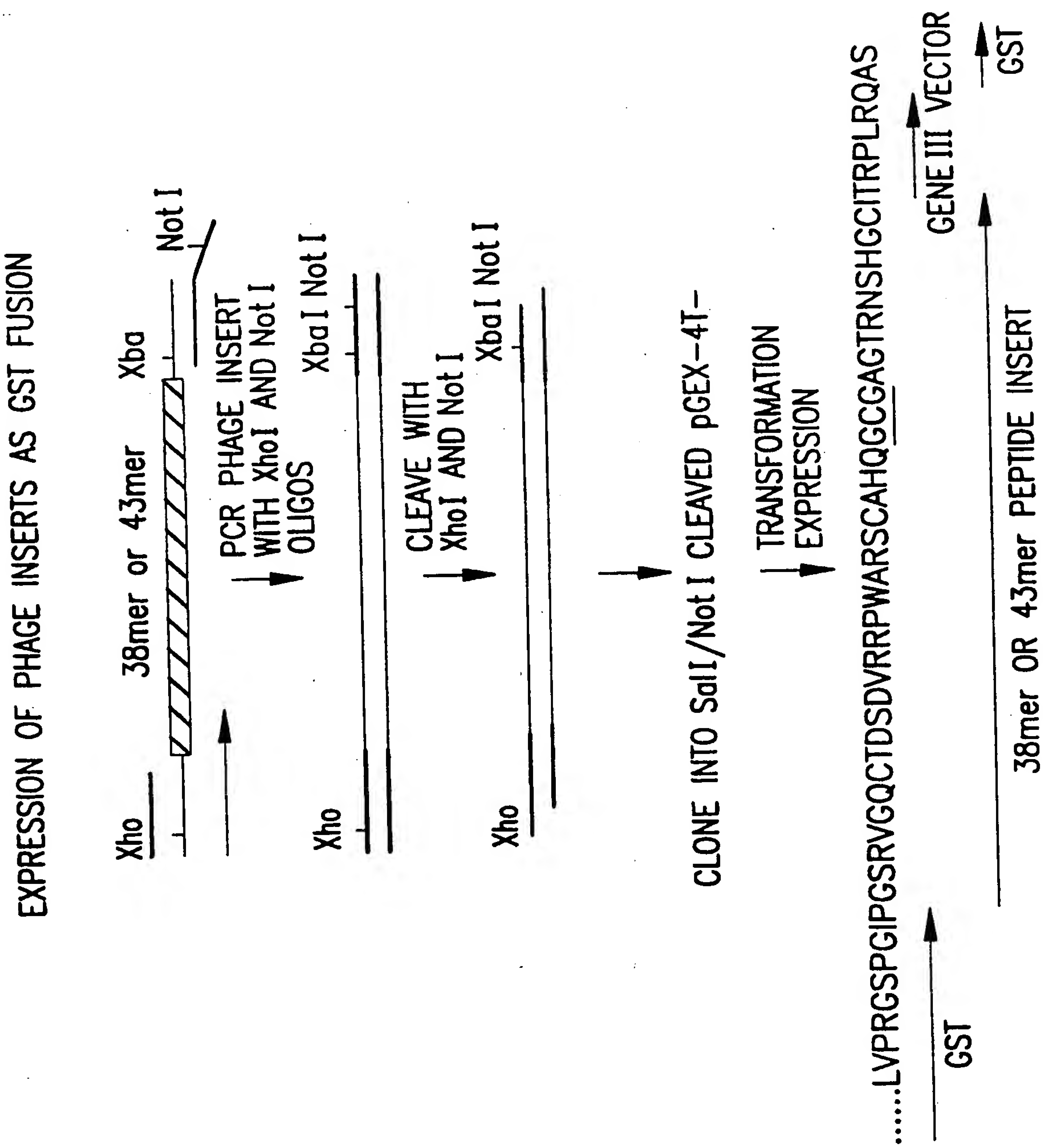

EXPRESSION OF PHAGE INSERTS AS GST FUSION
Xho
38mer or 43mer
Xba
Not I
PCR PHAGE INSERT WITH XhoI AND Not I OLIGOS
Xho
XbaI Not I
CLEAVE WITH XhoI AND Not I
Xho
XbaI Not I
CLONE INTO SalI/Not I CLEAVED pGEX-4T-
TRANSFORMATION EXPRESSION
......LVPRGSPGIPGSRVGQCTDSDVRRPWARSCAHQGCGAGTRNSHGCITRPLRQAS
GST
GENE III VECTOR
38mer OR 43mer PEPTIDE INSERT
GST

FIG.5A

```
P31  1         10         20         30                  Clone #
     |         |          |          |
     SARDSGPAEDGSRAVRLNGVENANTRKSSRSNPRGRRHP
     SARDSGPAEDGSRAVRLNG                                    101
              DGSRAVRLNGVENANTRKSSR                         102
                          ENANTRKSSRSNPRGRRHP               103
                              TRKSSRSNPRG                   119

Pax2 1         10         20         30                  Clone #
     |         |          |          |
     STPPSREAYSRPYSVDSDSDTNAKHSSHNRRLRTRSRPN
     STPPSREAYSRPYSVDSDSD                                   104
              SRPYSVDSDSDTNAKHSSHNR                         105
                          TNAKHSSHNRRLRTRSRPN               106

DCX8 1         10         20         30                  Clone #
     |         |          |          |
     RYKHDIGCDAGVDKKSSSVRGGCGAHSSPPRAGRGPRGTMVSRL
     RYKHDIGCDAGVDKKSSSVRGGCG                               107
           GCDAGVDKKSSSVRGGCGAHSSPPRA                       108
                              GAHSSPPRAGRGPRGTMVSRL         109
```

FIG.5B

```
P31   1         10          20          30                      Clone #
      |         |           |           |
      SARDSGPAEDGSRAVRLNGVENANTRKSSRSNPRGRRHP
                          ENANTRKSSRSNPRGRRHP                    103
                          ENANTRKSSR                             110
                              TRKSSRSNPRG                        119
                               RKSSRSNPRG                        111
                                 SNPRGRRHP                       112

Pax2  1         10          20          30                      Clone #
      |         |           |           |
      STPPSREAYSRPYSVDSDSDTNAKHSSHNRRLRTRSRPN
                          TNAKHSSHNRRLRTRSRPN                    106
                          TNAKHSSHN                              113
                               SSHNRRLRTR                        114
                                   RRLRTRSRPN                    115

SNi10 1         10          20          30                      Clone#
      |         |           |           |
      RVGQCTDSDVRRPWARSCAHQGCGAGTRNSHGCITRPLRQASAH
      RVGQCTDSDVRRPWARSCA                                        116
               VRRPWARSCAHQGCGAGTRNS                             117
                             GTRNSHGCITRPLRQASAH                 118
```

FIG.5C

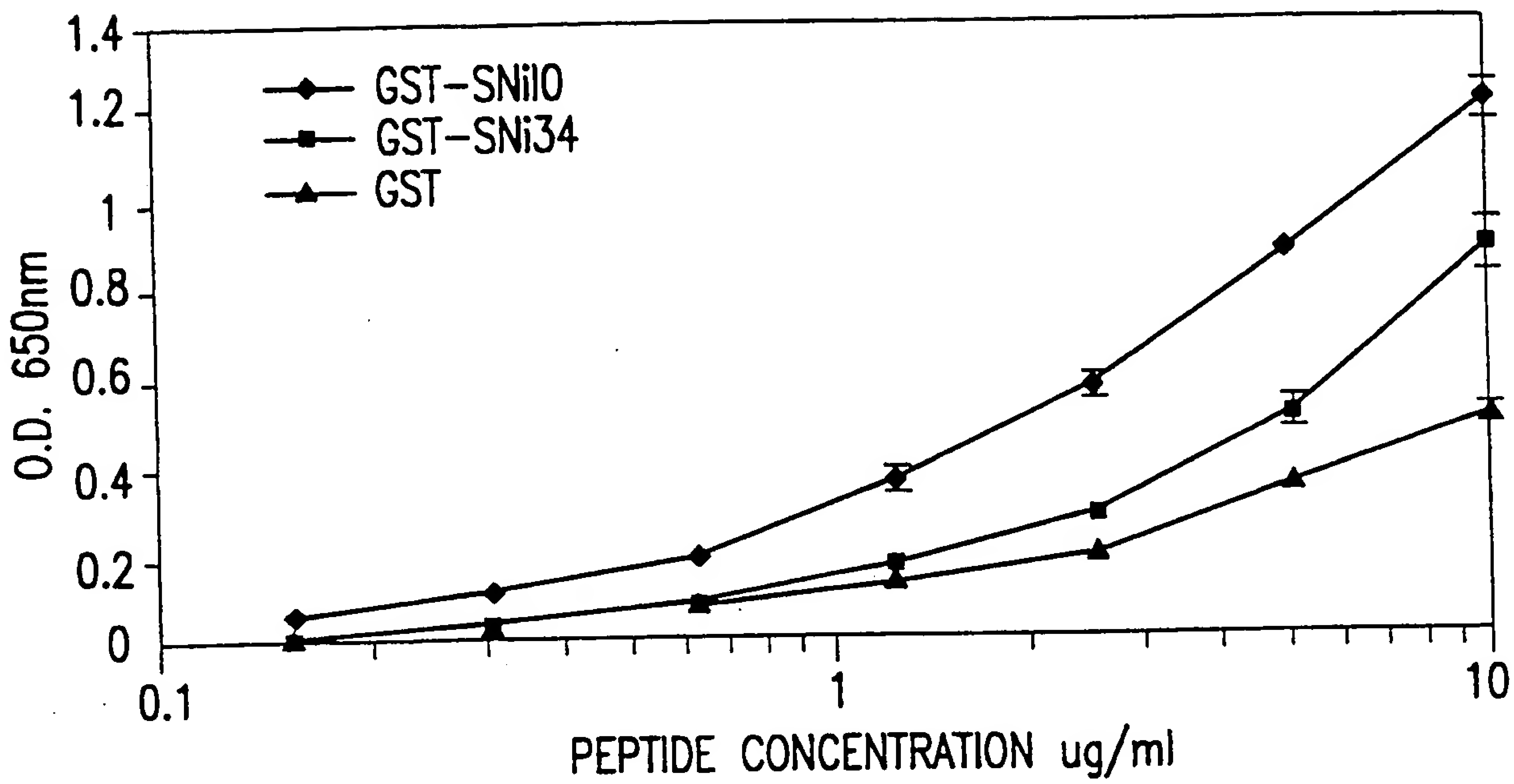

GST-SNil0
GST-SNi34
GST
O.D. 650nm
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0.1
1
10
PEPTIDE CONCENTRATION ug/ml

FIG.6A

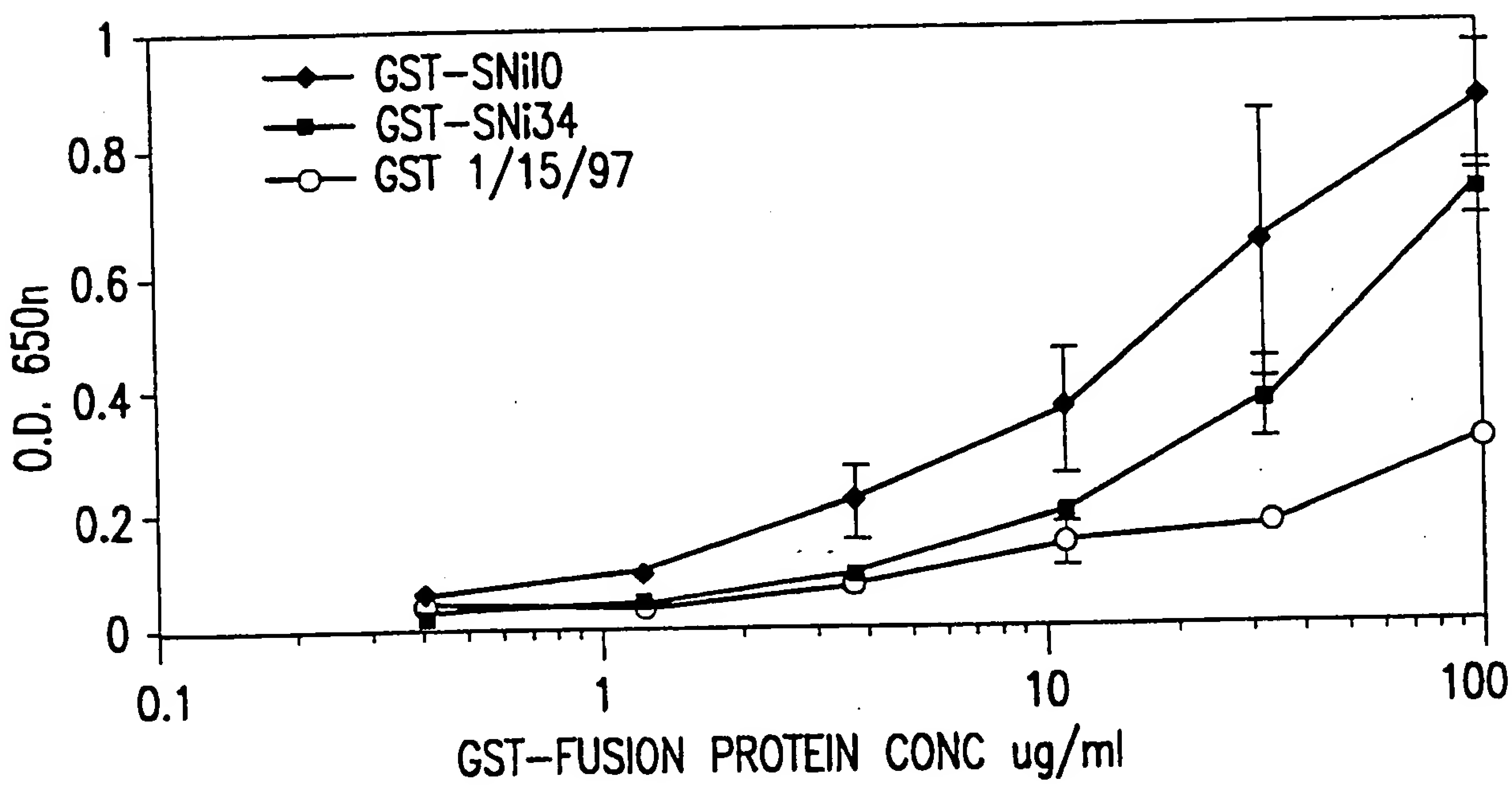
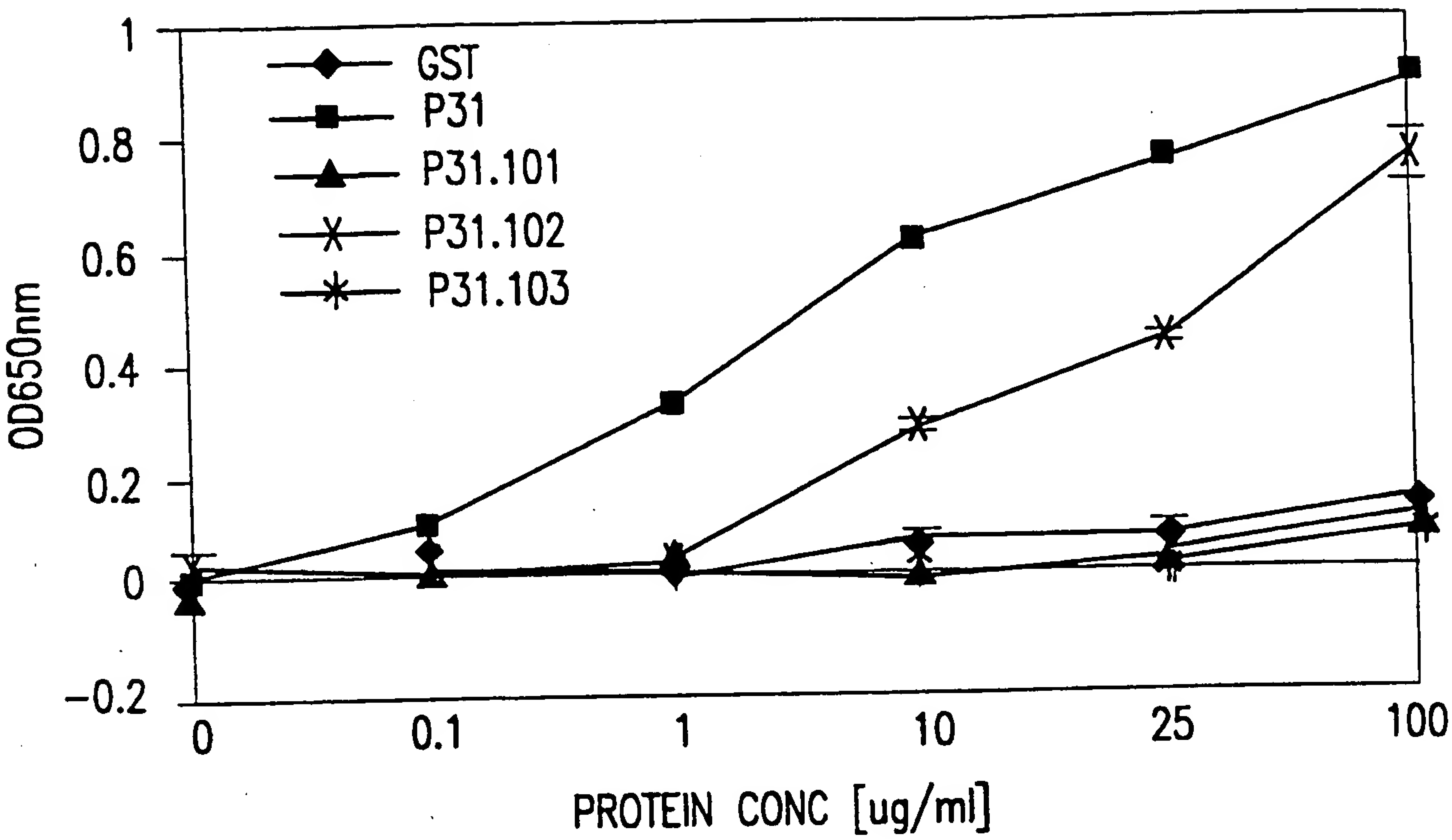
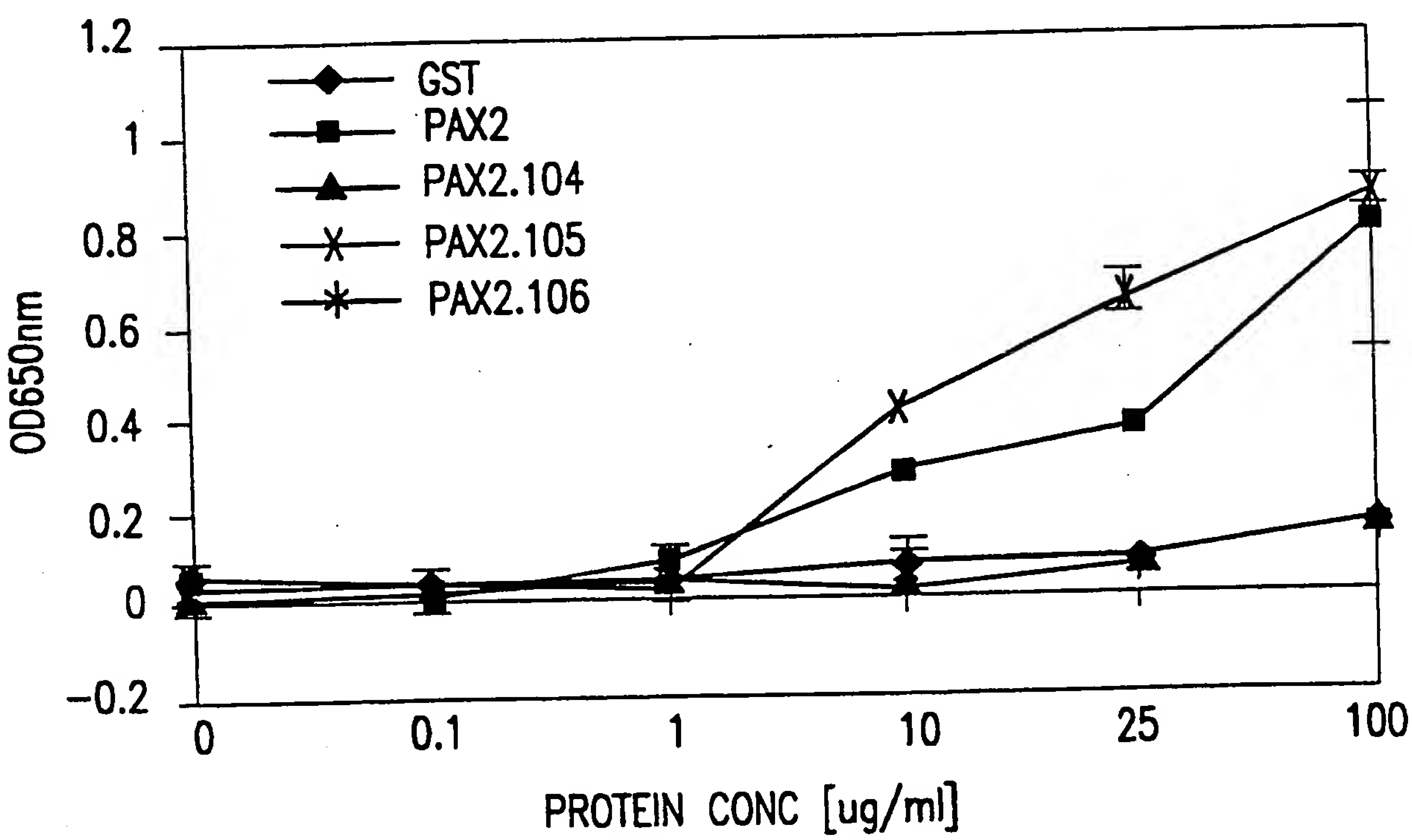

GST-SNil0
GST-SNi34
GST 1/15/97
O.D. 650n
1
0.8
0.6
0.4
0.2
0
0.1
1
10
100
GST-FUSION PROTEIN CONC ug/ml

FIG.6B



OD650nm
1
0.8
0.6
0.4
0.2
0
-0.2
GST
P31
P31.101
P31.102
P31.103
0
0.1
1
10
25
100
PROTEIN CONC [ug/ml]

FIG. 7A



OD650nm
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
GST
PAX2
PAX2.104
PAX2.105
PAX2.106
0
0.1
1
10
25
100
PROTEIN CONC [ug/ml]

FIG. 7B

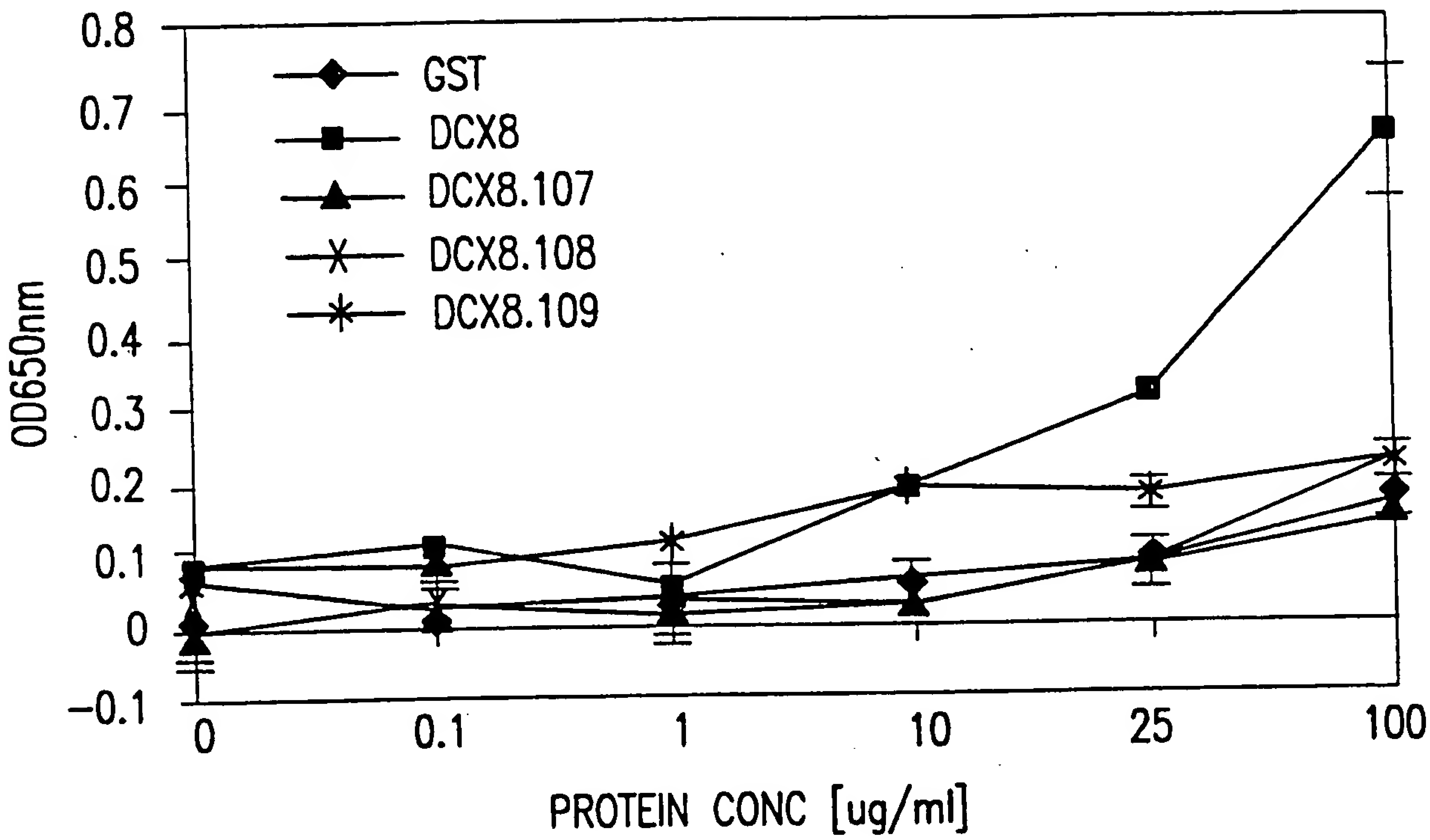

0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
OD650nm
GST
DCX8
DCX8.107
DCX8.108
DCX8.109
0
0.1
1
10
25
100
PROTEIN CONC [ug/ml]

FIG. 7C

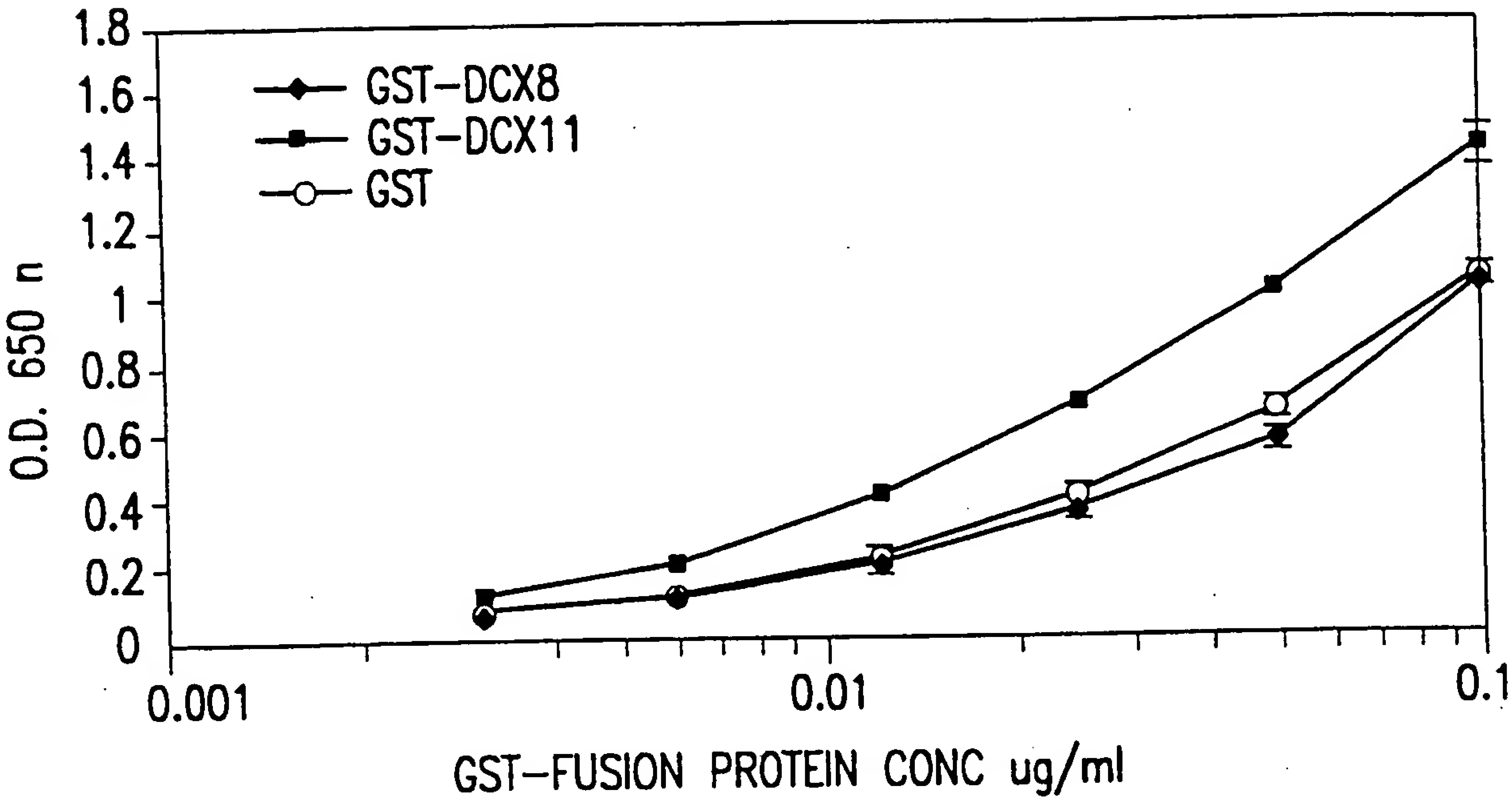

1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
O.D. 650 n
GST-DCX8
GST-DCX11
GST
0.001
0.01
0.1
GST-FUSION PROTEIN CONC ug/ml

FIG.7D

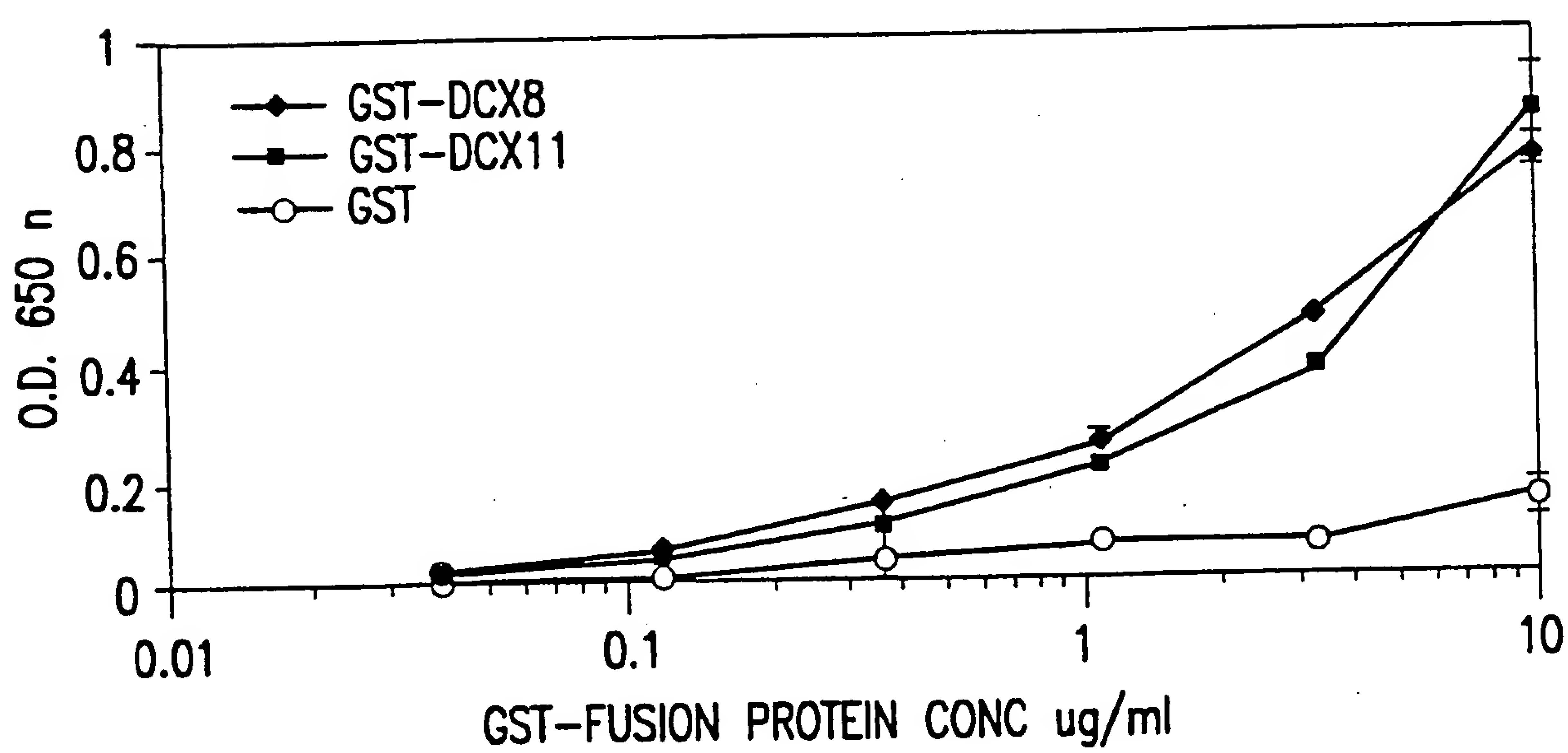

1
0.8
0.6
0.4
0.2
0
O.D. 650 n
GST-DCX8
GST-DCX11
GST
0.01
0.1
1
10
GST-FUSION PROTEIN CONC ug/ml

FIG.7E

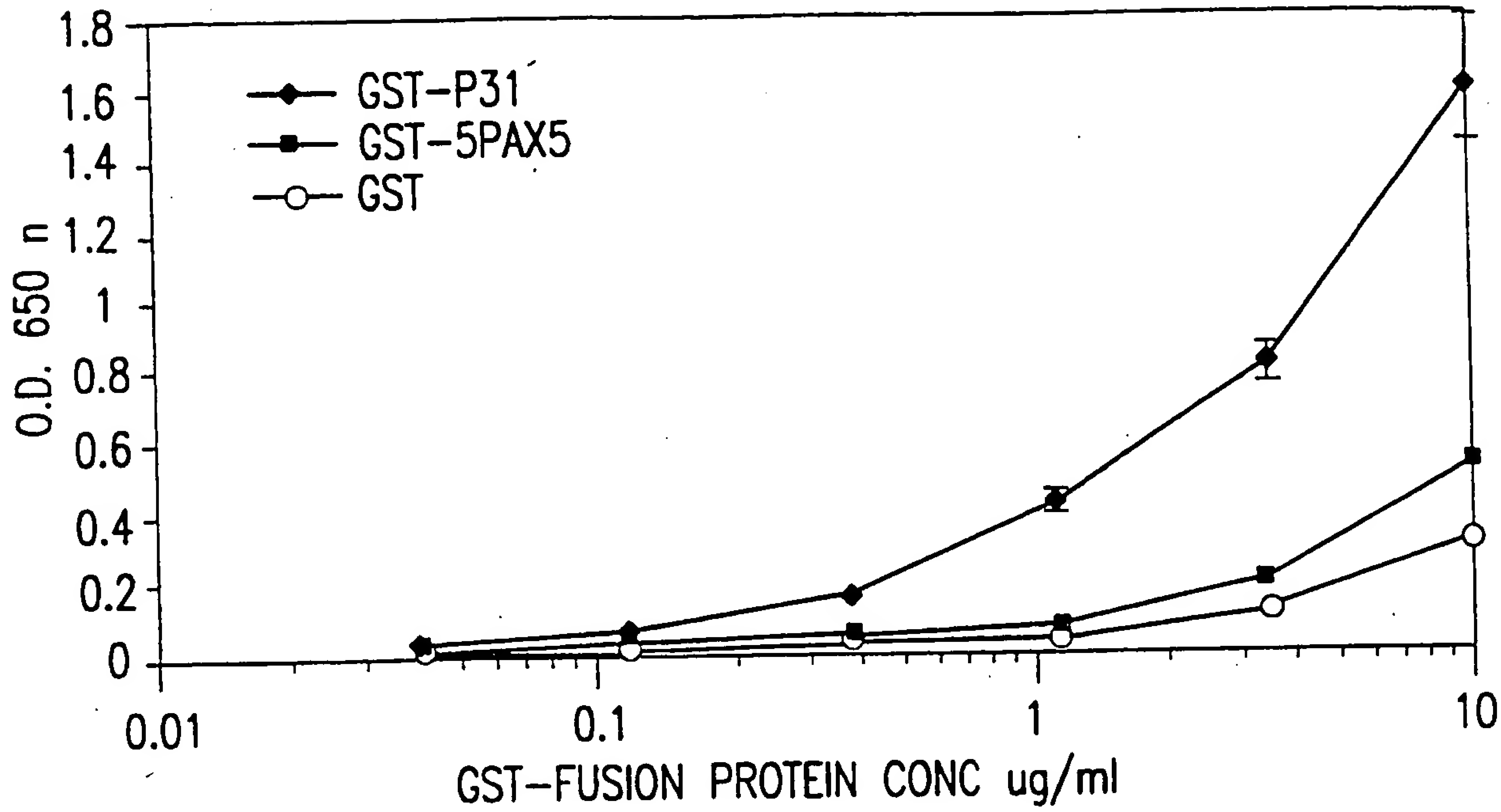

1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
O.D. 650 n
GST-P31
GST-5PAX5
GST
0.01
0.1
1
10
GST-FUSION PROTEIN CONC ug/ml

FIG.7F

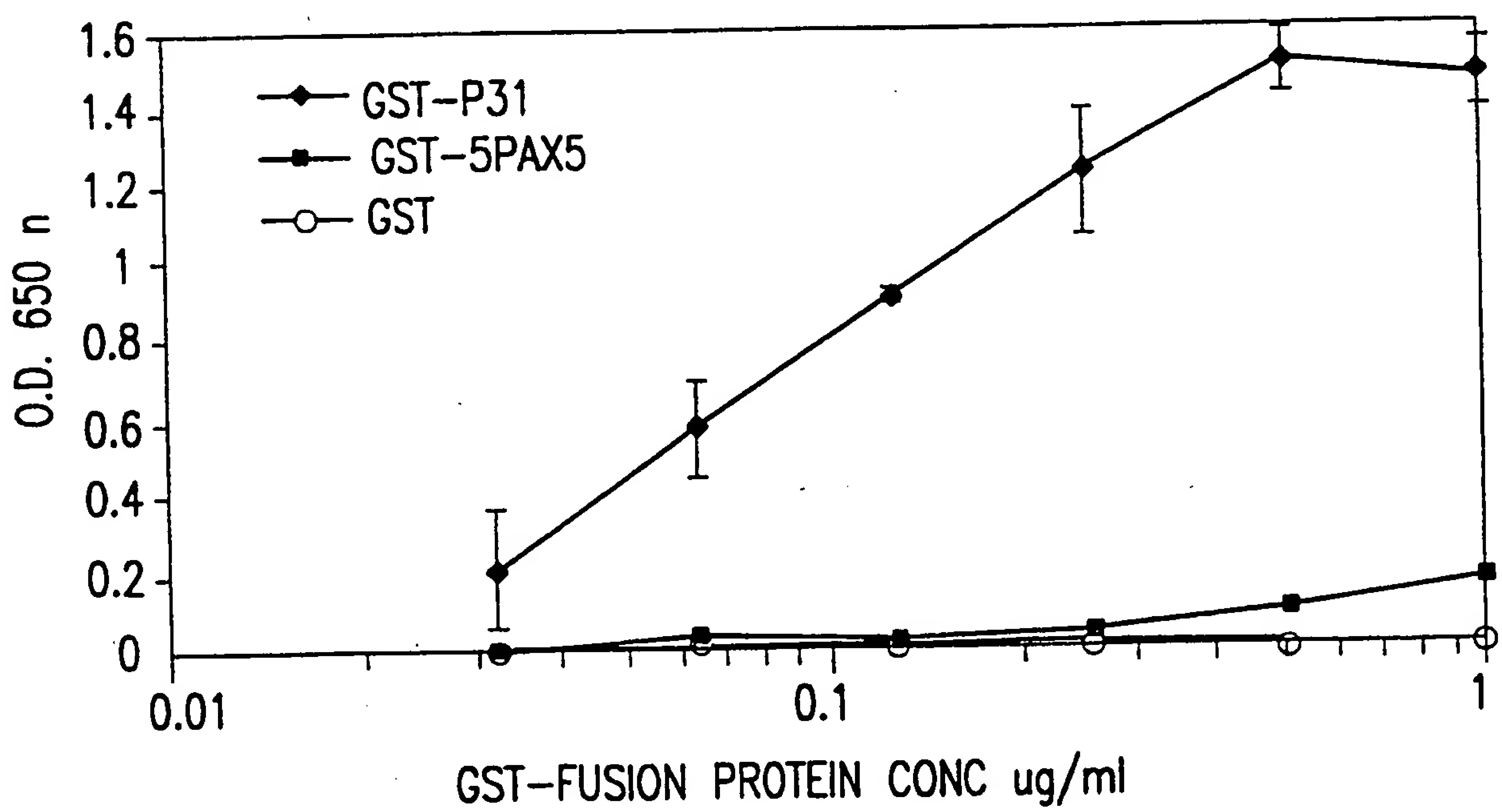

1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
O.D. 650 n
GST-P31
GST-5PAX5
GST
0.01
0.1
1
GST-FUSION PROTEIN CONC ug/ml

FIG.7G

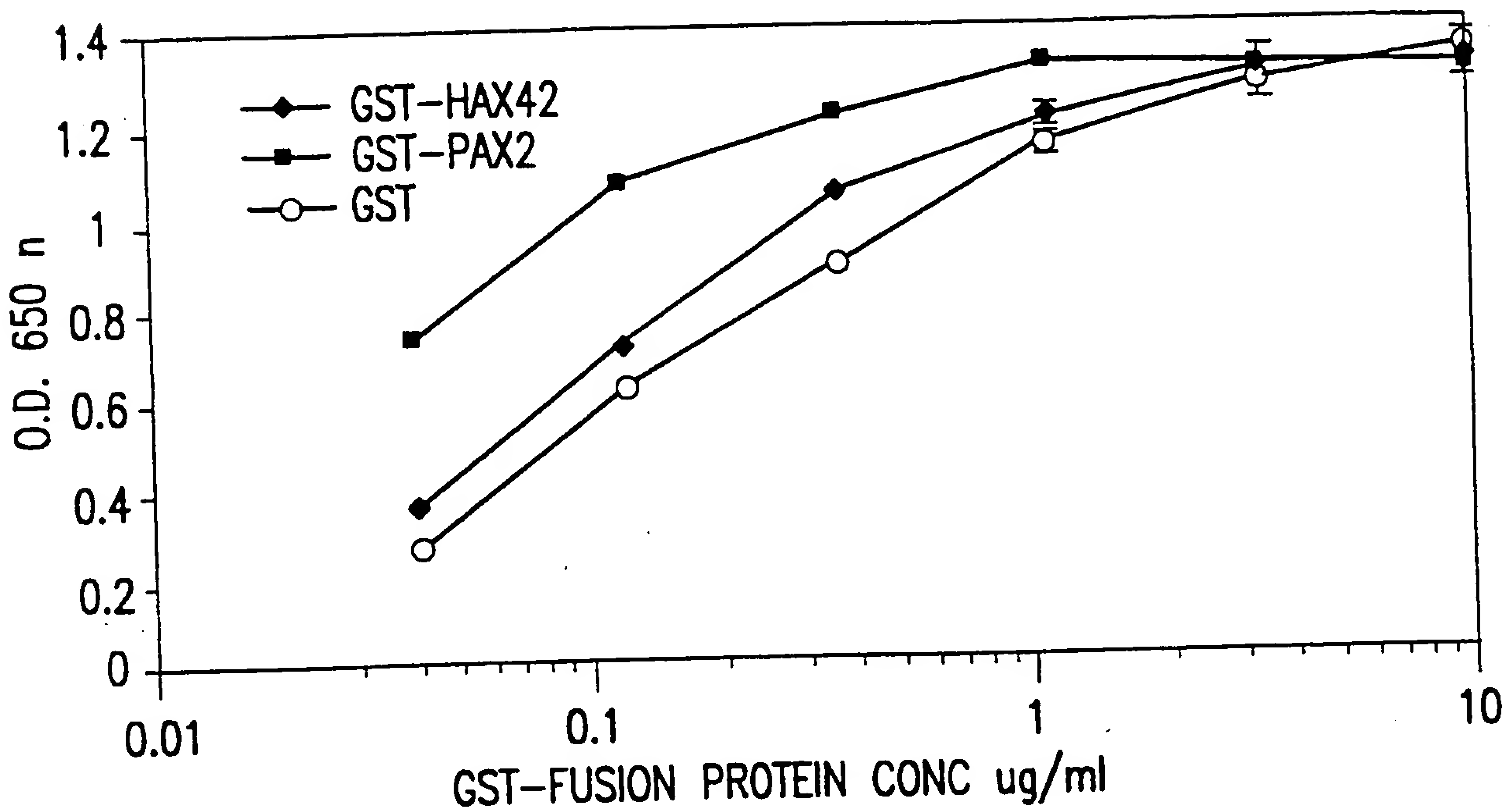

1.4
1.2
1
0.8
0.6
0.4
0.2
0
O.D. 650 n
GST-HAX42
GST-PAX2
GST
0.01
0.1
1
10
GST-FUSION PROTEIN CONC ug/ml

FIG.7H

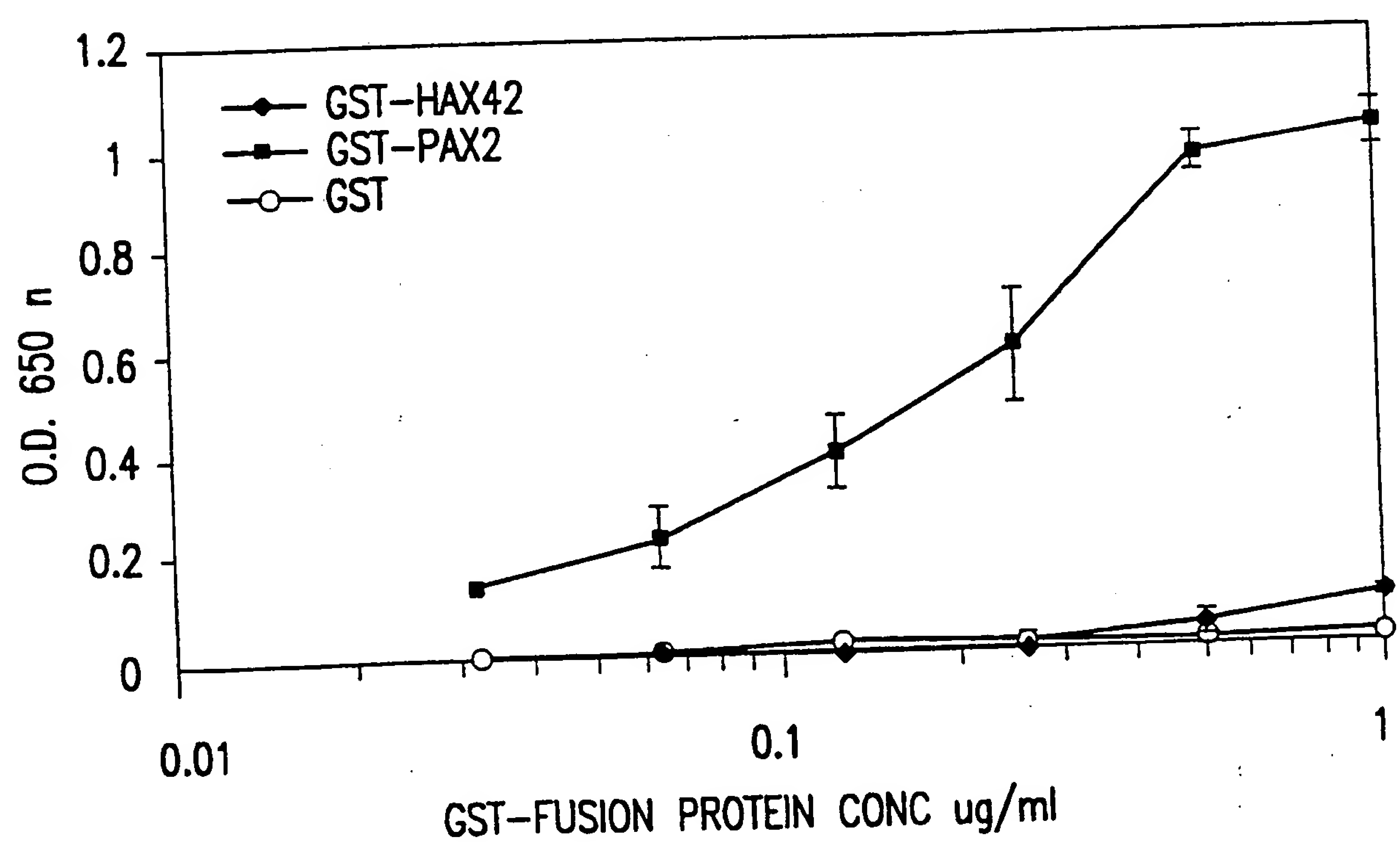

1.2
1
0.8
0.6
0.4
0.2
0
O.D. 650 n
GST-HAX42
GST-PAX2
GST
0.01
0.1
1
GST-FUSION PROTEIN CONC ug/ml

FIG.7I

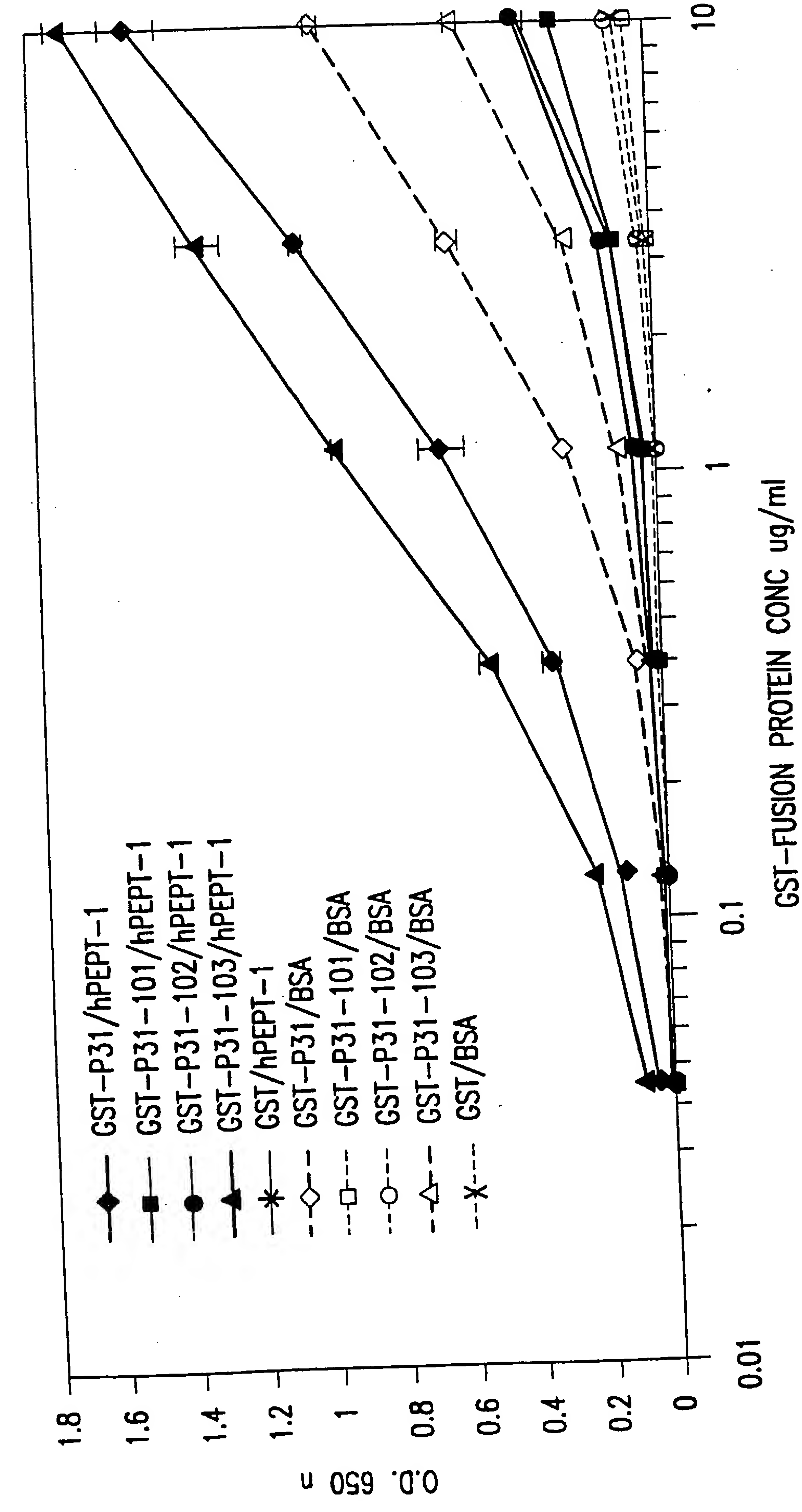

GST-P31/hPEPT-1
GST-P31-101/hPEPT-1
GST-P31-102/hPEPT-1
GST-P31-103/hPEPT-1
GST/hPEPT-1
GST-P31/BSA
GST-P31-101/BSA
GST-P31-102/BSA
GST-P31-103/BSA
GST/BSA
O.D. 650 n
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0.01
0.1
1
10
GST-FUSION PROTEIN CONC ug/ml

FIG. 7J

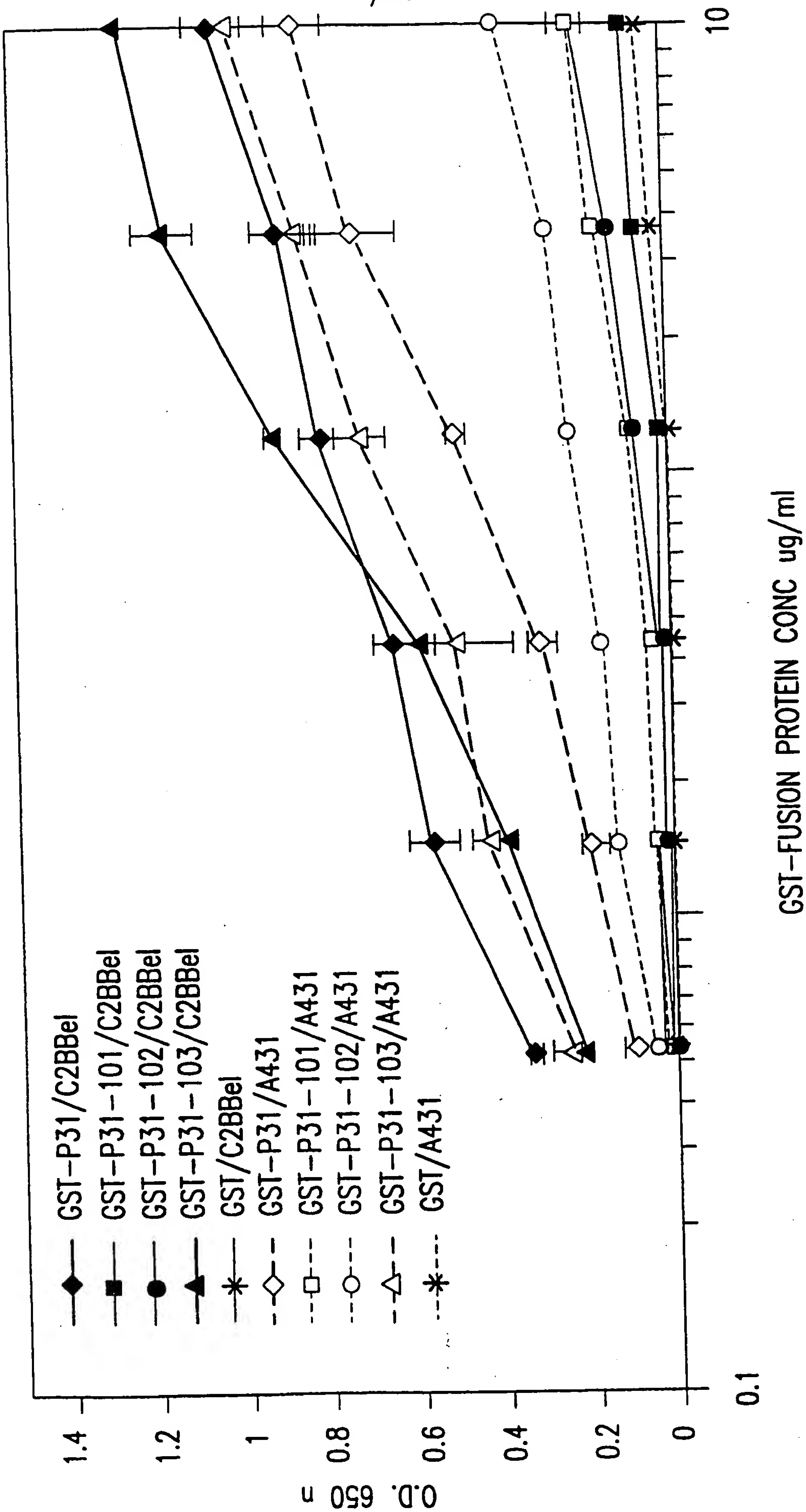

GST–P31/C2BBel
GST–P31–101/C2BBel
GST–P31–102/C2BBel
GST–P31–103/C2BBel
GST/C2BBel
GST–P31/A431
GST–P31–101/A431
GST–P31–102/A431
GST–P31–103/A431
GST/A431
O.D. 650 n
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0.1
10
GST–FUSION PROTEIN CONC ug/ml

FIG. 7K

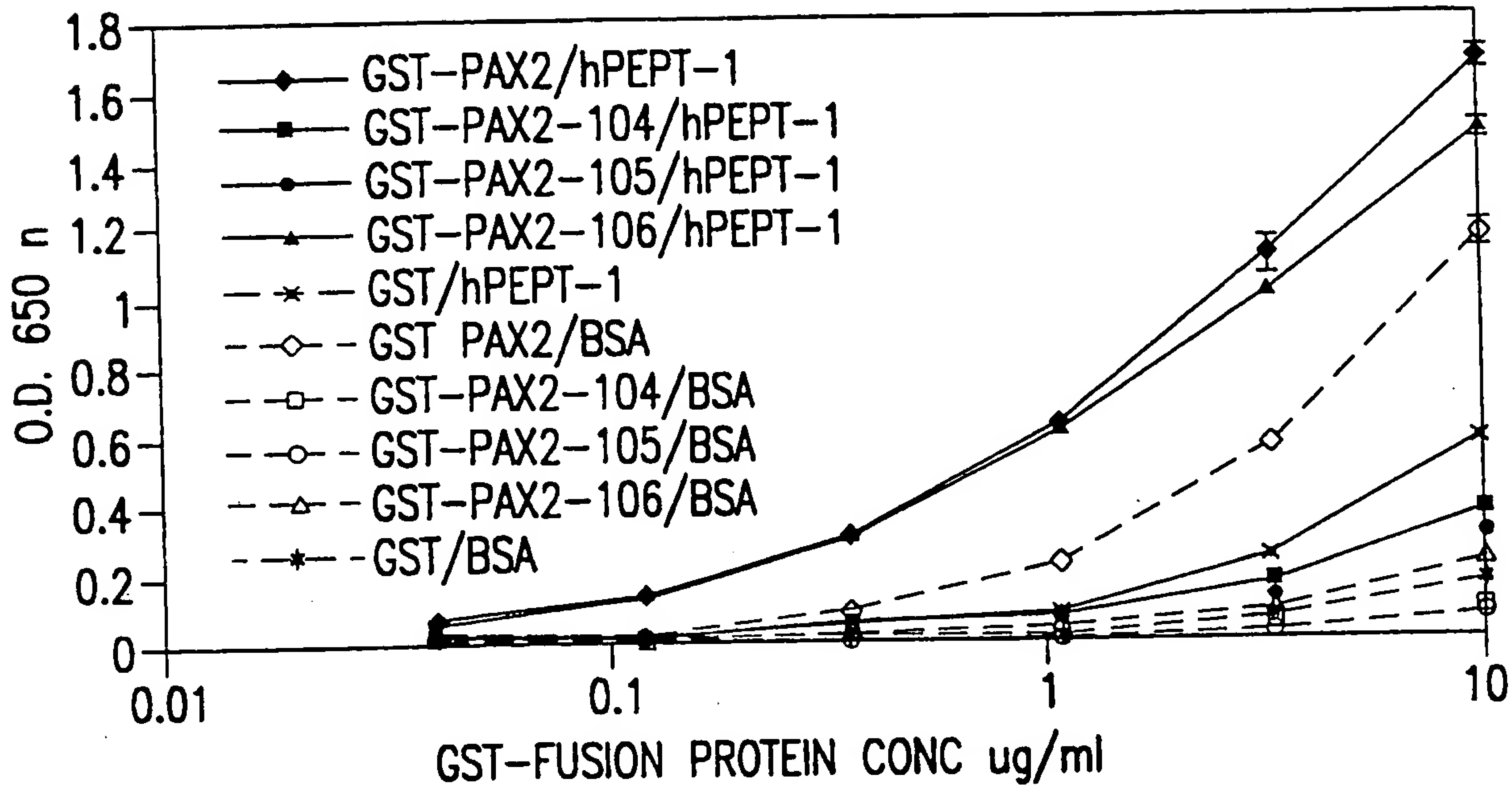

1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
O.D. 650 n
GST-PAX2/hPEPT-1
GST-PAX2-104/hPEPT-1
GST-PAX2-105/hPEPT-1
GST-PAX2-106/hPEPT-1
GST/hPEPT-1
GST PAX2/BSA
GST-PAX2-104/BSA
GST-PAX2-105/BSA
GST-PAX2-106/BSA
GST/BSA
0.01
0.1
1
10
GST-FUSION PROTEIN CONC ug/ml

FIG. 7L

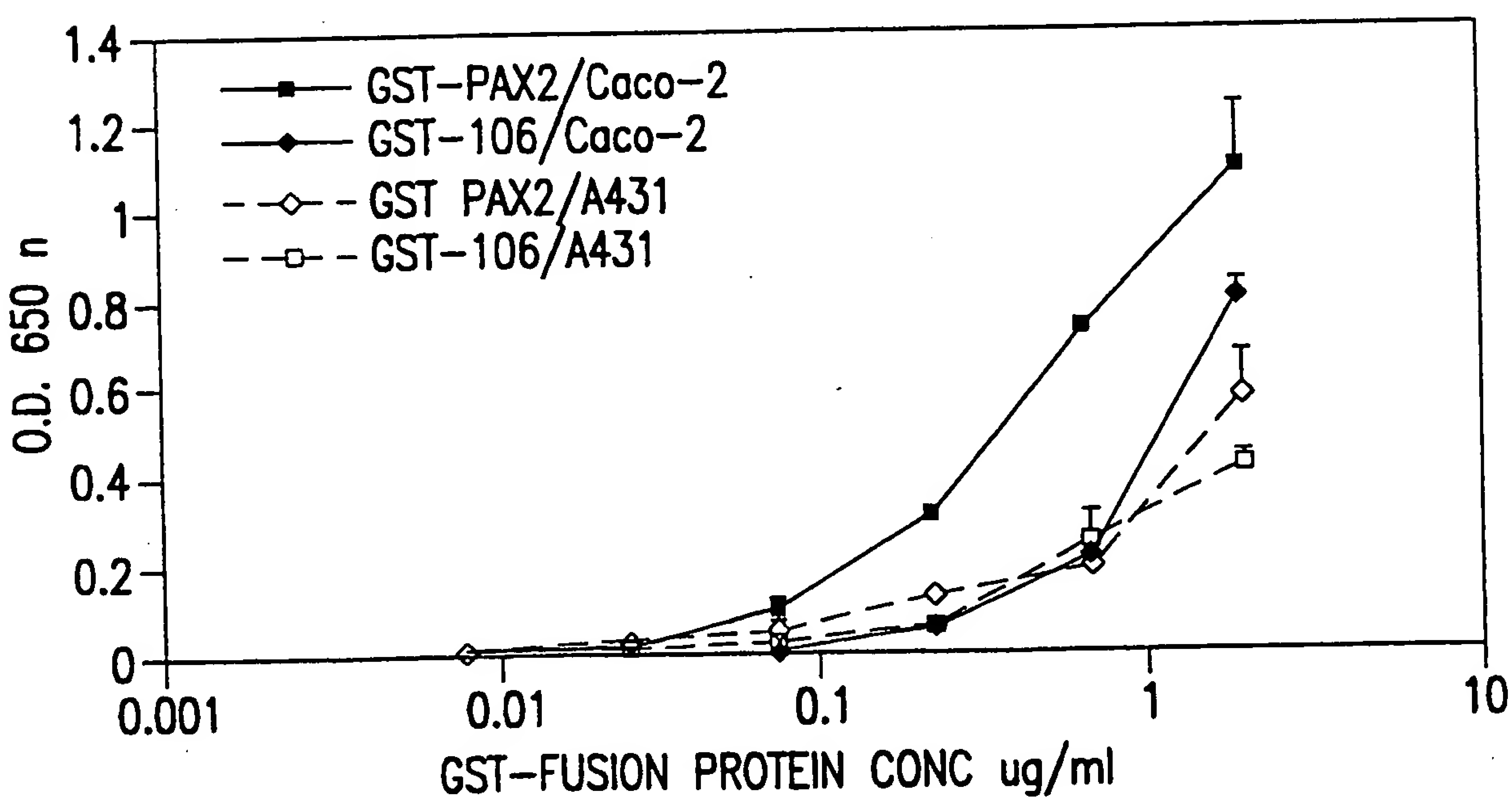
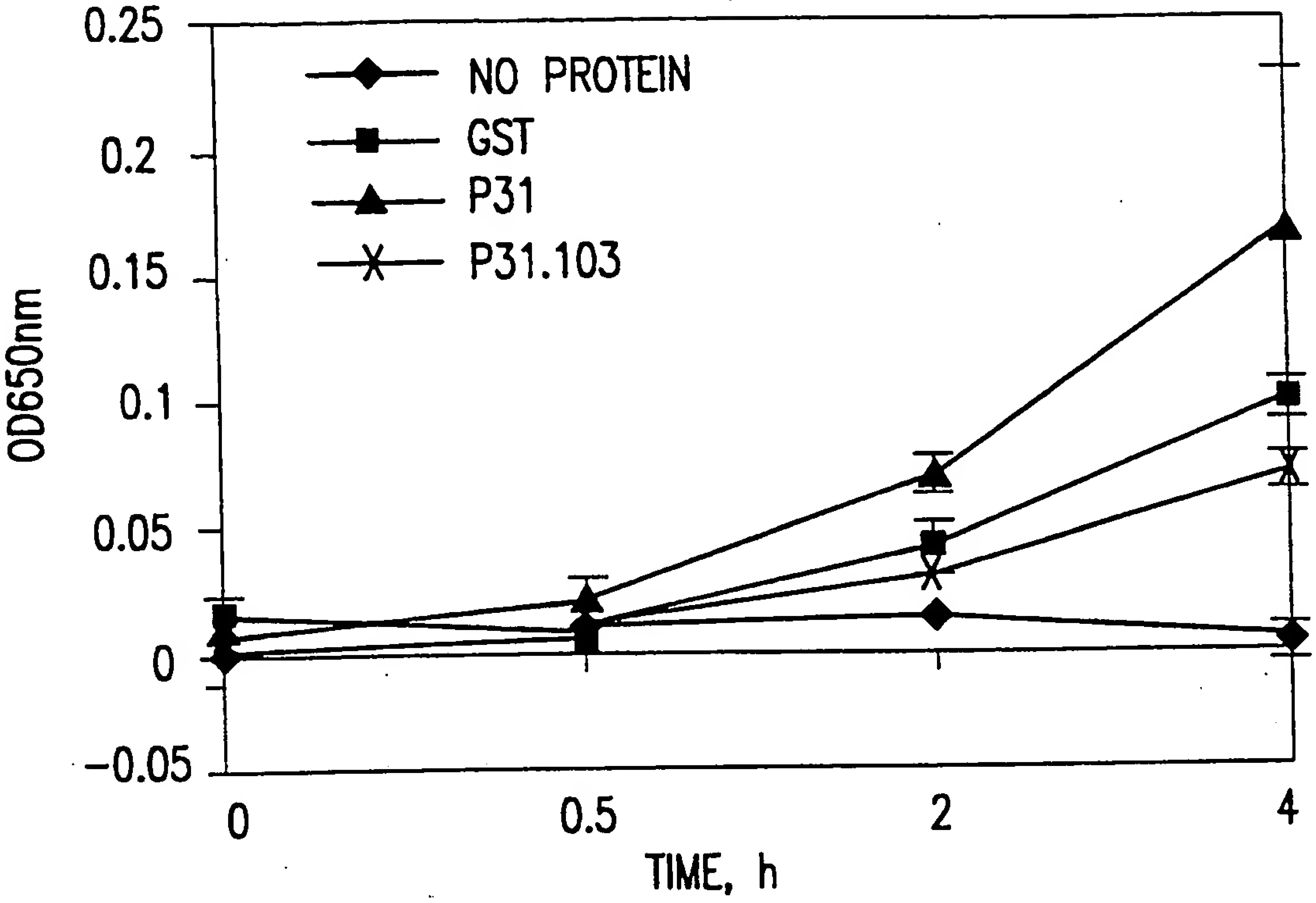
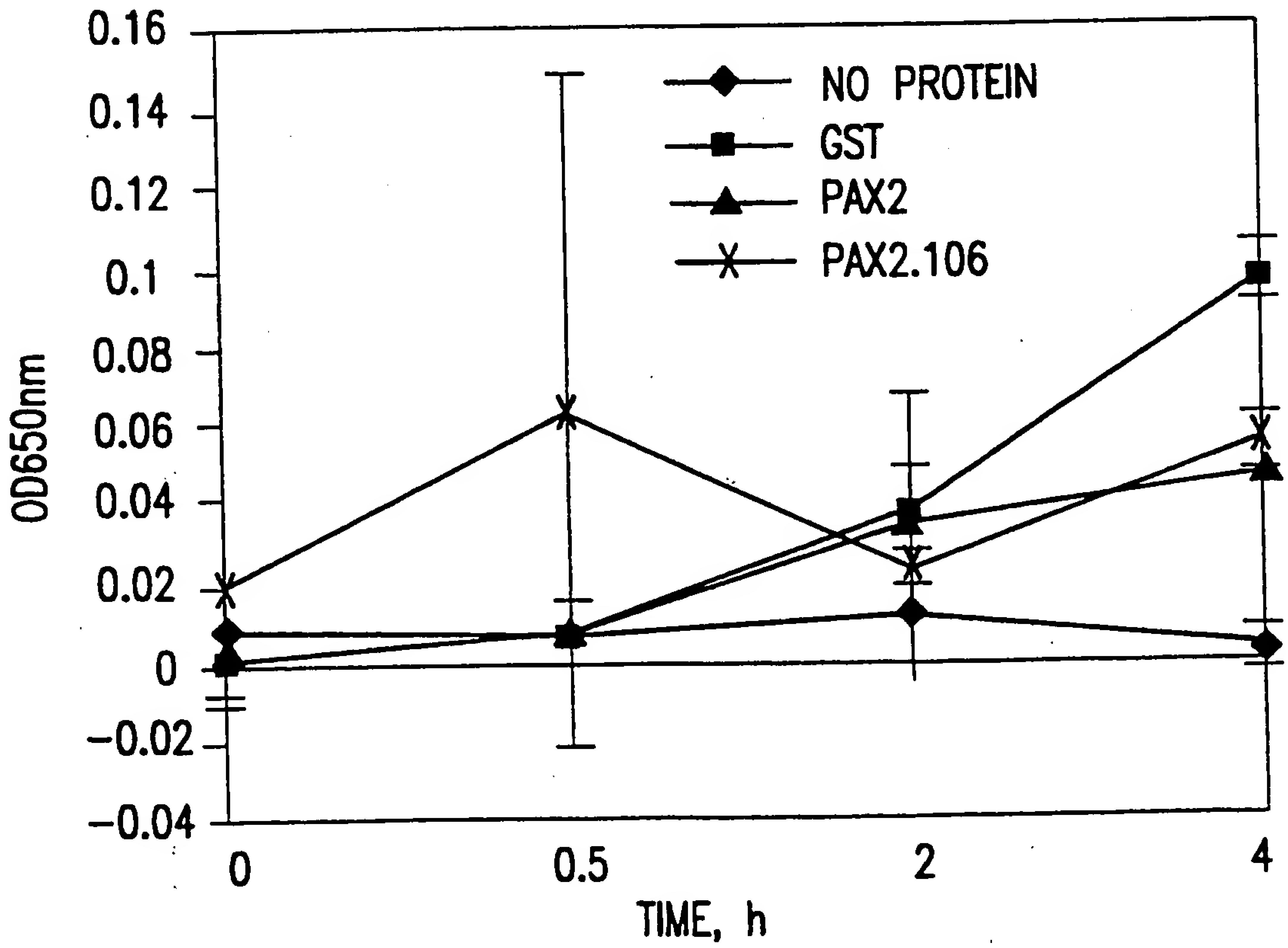

1.4
1.2
1
0.8
0.6
0.4
0.2
0
O.D. 650 n
GST-PAX2/Caco-2
GST-106/Caco-2
GST PAX2/A431
GST-106/A431
0.001
0.01
0.1
1
10
GST-FUSION PROTEIN CONC ug/ml

FIG. 7M



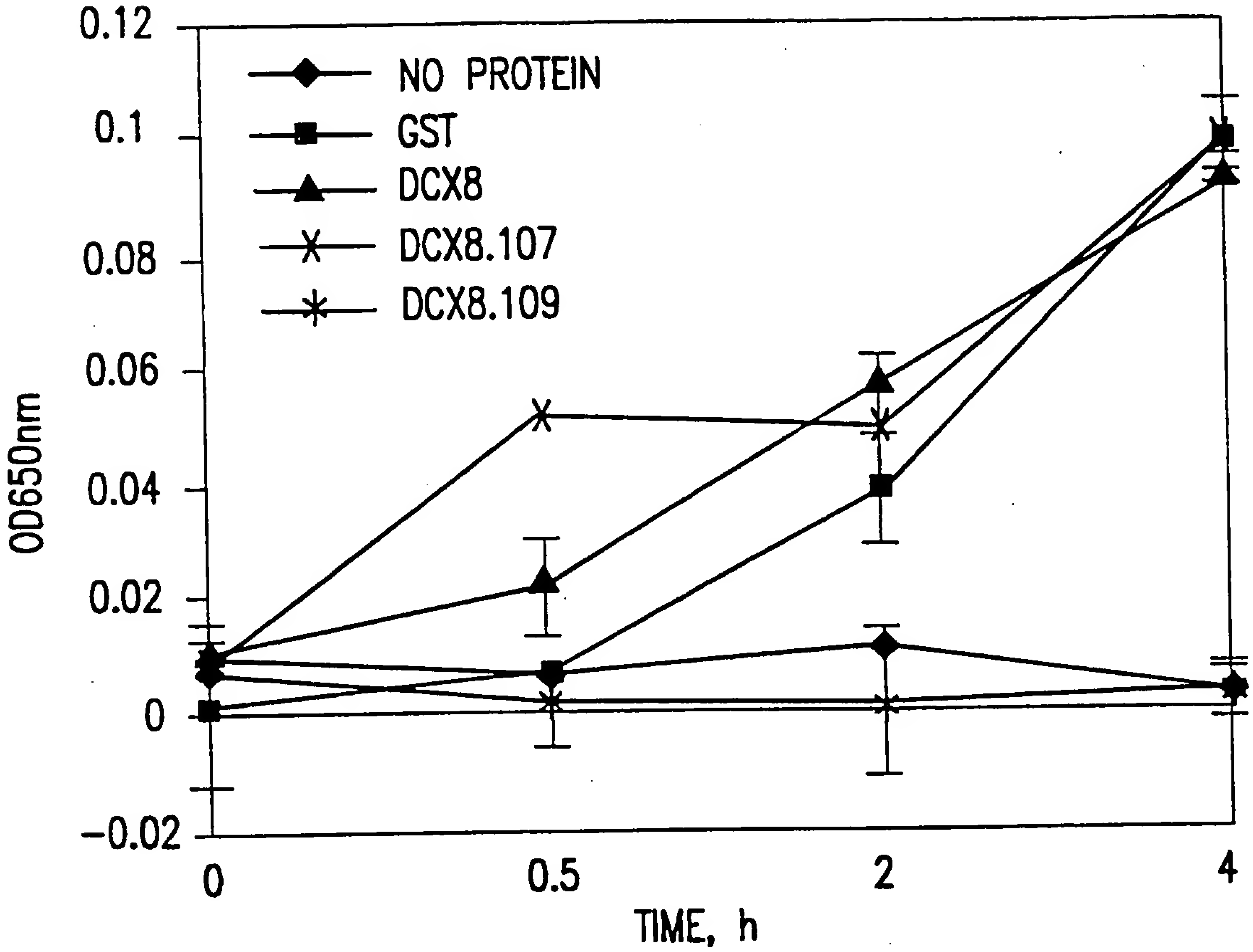
0.25
0.2
0.15
0.1
0.05
0
−0.05
OD650nm
NO PROTEIN
GST
P31
P31.103
0
0.5
2
4
TIME, h

FIG.8A



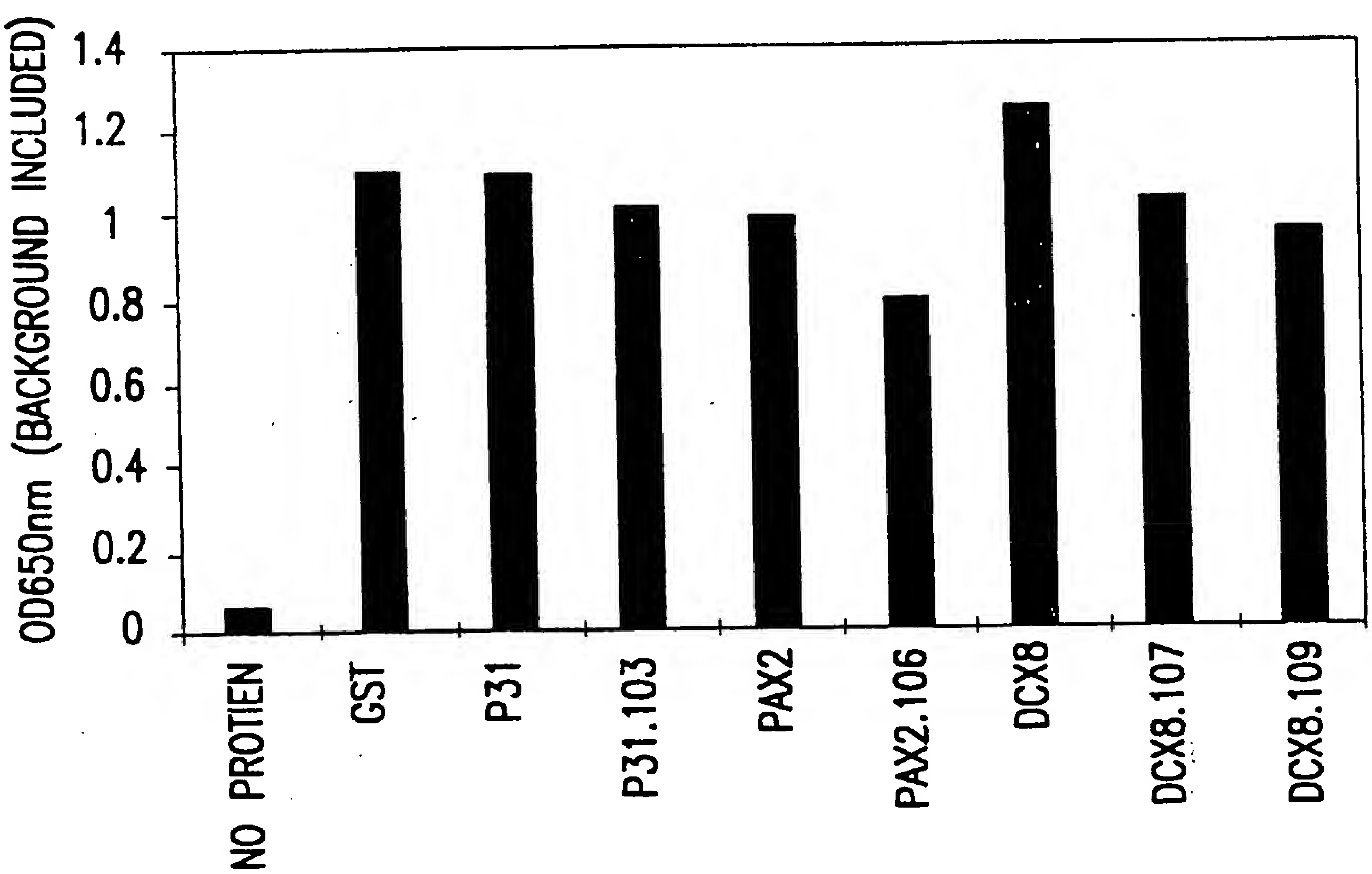
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
−0.02
−0.04
OD650nm
NO PROTEIN
GST
PAX2
PAX2.106
0
0.5
2
4
TIME, h

FIG.8B



0.12
0.1
0.08
0.06
0.04
0.02
0
-0.02
OD650nm
NO PROTEIN
GST
DCX8
DCX8.107
DCX8.109
0
0.5
2
4
TIME, h

FIG.8C



OD650nm (BACKGROUND INCLUDED)
1.4
1.2
1
0.8
0.6
0.4
0.2
0
NO PROTIEN
GST
P31
P31.103
PAX2
PAX2.106
DCX8
DCX8.107
DCX8.109

FIG.8D

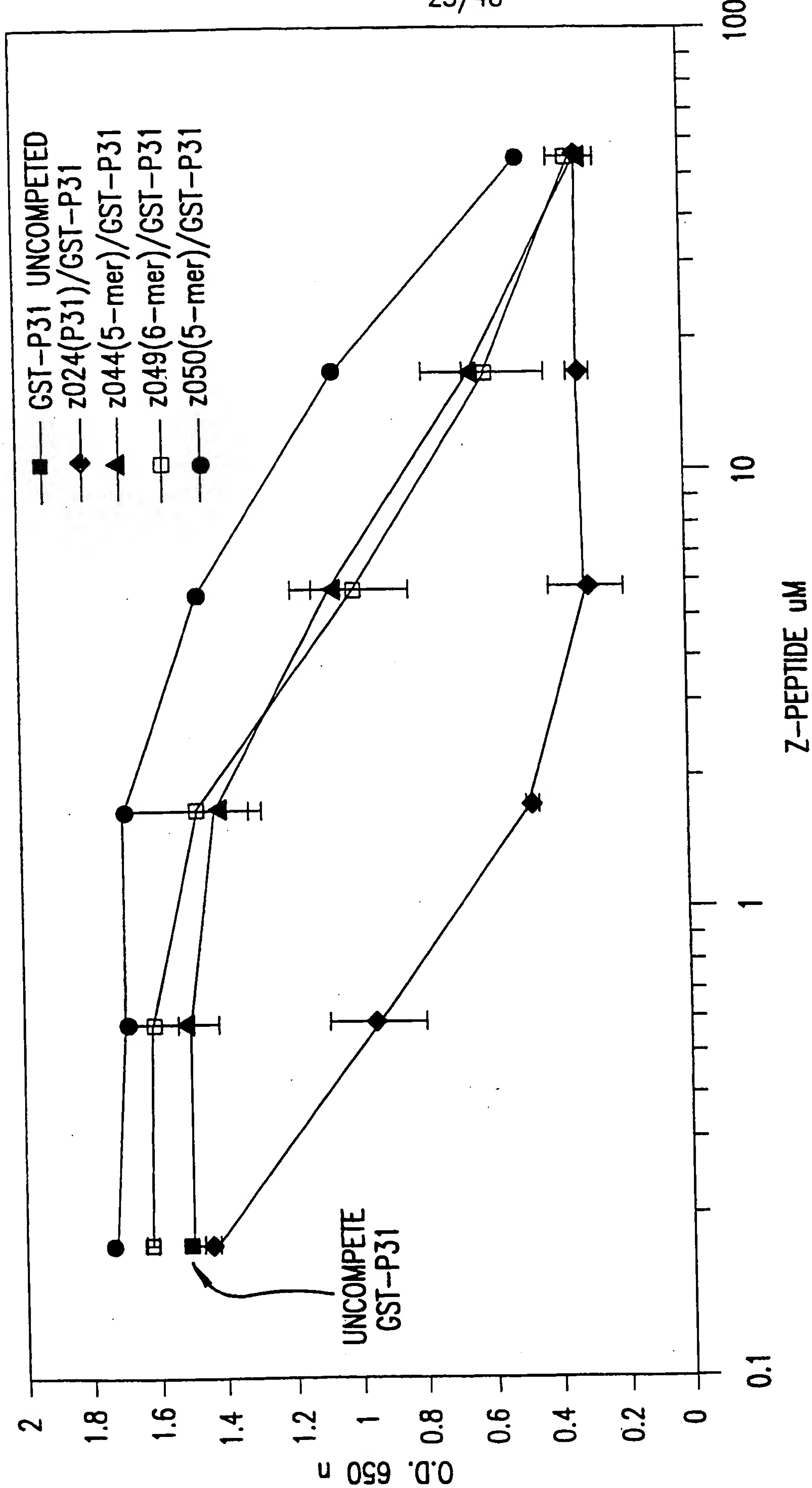

GST-P31 UNCOMPETED
z024(P31)/GST-P31
z044(5-mer)/GST-P31
z049(6-mer)/GST-P31
z050(5-mer)/GST-P31
UNCOMPETE
GST-P31
O.D. 650 n
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0.1
1
10
100
Z-PEPTIDE uM

FIG.9A

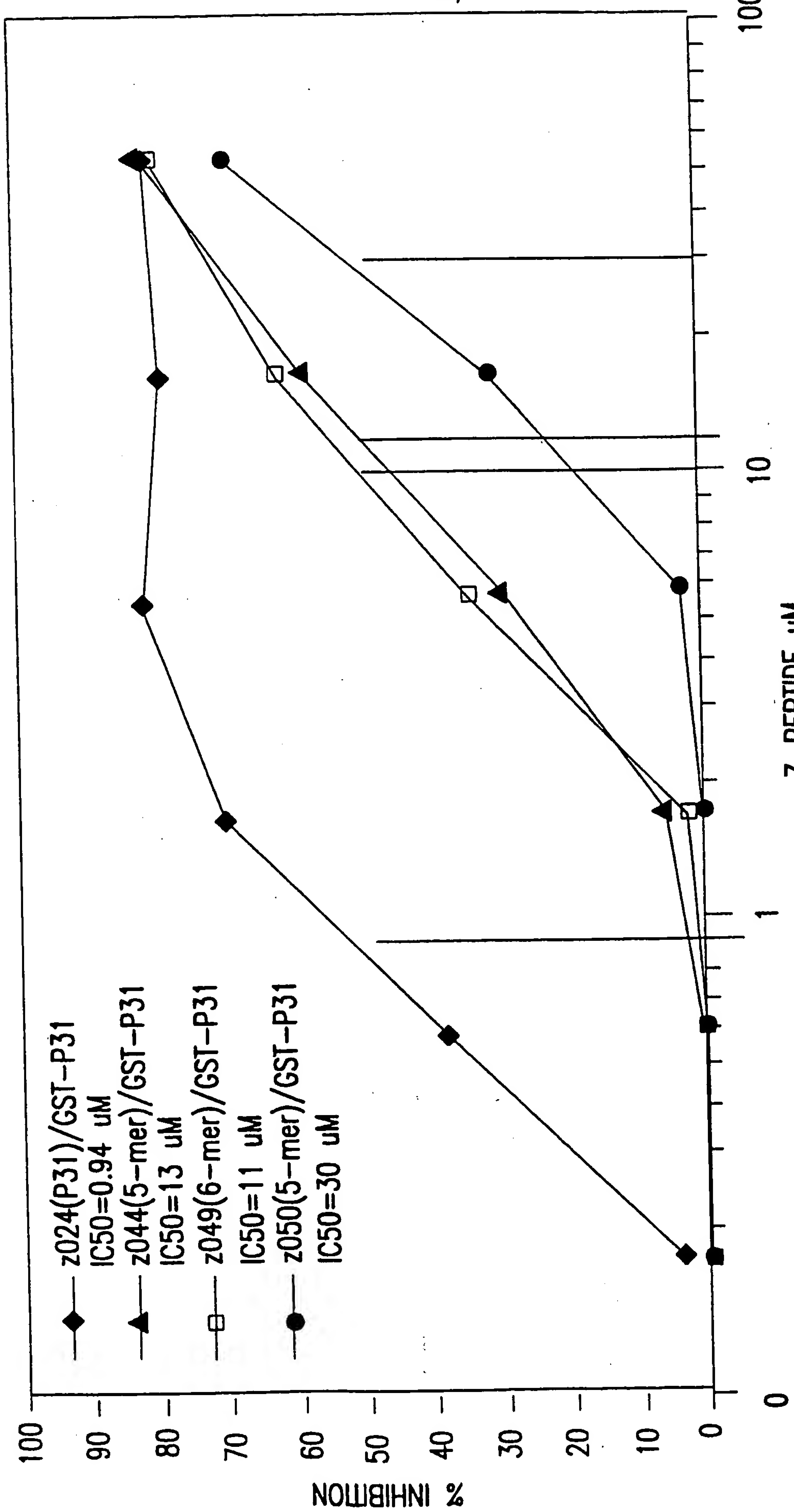

z024(P31)/GST–P31
IC50=0.94 uM
z044(5–mer)/GST–P31
IC50=13 uM
z049(6–mer)/GST–P31
IC50=11 uM
z050(5–mer)/GST–P31
IC50=30 uM
% INHIBITION
100
90
80
70
60
50
40
30
20
10
0
0
1
10
100
Z–PEPTIDE uM

FIG.9B

Peptide Name	Sequence	pI	IC50	GST/C2BBe1
	1 10 20 30 40			
ELAN024(P31)	SARDSGPAEDGSRAVRLNGVENANTRKSSRSNPRGRRHPG	11.88	0.5-2.2	+++ -
101	SARDSGPAEDGSRAVRLNG			-
102	DGSRAVRLNGVENANTRKSSR			++
103	ENANTRKSSRSNPRGRRHP			-
110	ENANTRKSSR			-
111	RKSSRSNPRG			-
112	SNPRGRRKP			
119	TRKSSRSNPRG			
Z28	ZENANTRKSSRSNPRGRRHPG	12.28	0.5-1.7	
Z29	ZTRKSSRSNPRG	12.40	5.5-15	
Z30	ZENANTRKSSRSNPRG	11.81	> 50	
Z31	ZTRKSSRSNPRGRRHPG	12.70	0.6-3.2	
Z39	ZENANTRKSSR	10.89	> 50	
Z40	ZSNPRGRRHPG	12.40	5.9-29	
Z41	ZENANT	3.75	>50	
Z42	ZANTRKS	11.05	>50	
Z43	ZTRKSS	11.05	>50	
Z44	ZRKSSR	12.11	13- > 50	
Z45	ZKSSRSN	11.05	40-48	
Z46	ZSSRSNPG	10.04	>50	
Z47	ZRSNPRG	12.40	>50	
Z48	ZSNPRG	10.04	>50	
Z49	ZPRGRRH	12.40	11-20	
Z50	ZRRHPG	12.10	30	
Z51 (HepC core)	ZKSSRGN	12.40	>50	
Z52 (HepC p26664)	ZKTSERSQPRGRRQPG	12.10	9.8	
Z53	ZTrKSSrSNPrGrrHPG		1.6	
Z54	ZTRKSSrSNPRGrRHPG		1.6	
Z21(HAX42)	SDHALGTNLRSDNAKEPGDYNCCGNGNSTGRKVFNRRRPSAIPT	11.27	1.7	

FIG.10A

Peptide Name	Sequence (1, 10, 20, 30, 40)	pI	IC50	GST/C2BBel
ELAN018(PAX2)	STPPSREAYSRPYSVDSDSDTNAKHSSHNRRLRTRSRPNG	10.88	0.6-0.9. 1	+++
104	STPPSREAYSRPYSVDSDSD			-
105	SRPYSVDSDSDTNAKHSSHNR			-
106	TNAKHSSHNRRLRTRSRPN			++
113	TNAKHSSHN			-
114	SSHNRRLRTR			+/-
115	RRLRTRSRPN			+/-
Z32	ZTNAKHSSHNRRLRTRSRPN	12.7	1.2	
Z33	ZTNAKHSSHNRRLRTR	12.58	1.6	
Z34	ZSSHNRRLRTRSRPN	12.7	1.6. 1.3. 0.68. 1.5	
Z35	ZSSHNRRLRTR	12.58	0.38 - 1.8 . 2.7	
Z26	ZSEANLDGRKSRYSSPRRNSSTRPRTSPNSVHARYPSTDHD	10.88	7-8. 3	
Z38	ZSRANTDGRKSRYSSPRRNSSTEPRLSPNSVHARYPSTDHD	10.88	1.7. 0.9	
Z55	ZTNAKHSSHN		42	
Z56	ZRRLRTRSRPN		1.7	
Z57	ZRRLRTRSRP		1.9	
Z58	ZRRLRTR		3.4	
Z59	ZrrLrTrSrPN		NOT DONE	
Z73	ZASHNRRLRTR		1.5. 5.5	
Z74	ZSAHNRRLRTR		6.2	
Z75	ZSSANRRLRTR		1.6	
Z76	ZSSHARRLRTR		1.8	
Z77	ZSSHNARLRTR		3.9. 5.2	
Z78	ZSSHNRALRTR		4.5. 4.6	
Z79	ZSSHNRRARTR		1.4	
Z80	ZSSHNRRLATR		3.4. 5.2	
Z81	ZSSHNRRLRAR		2.2	
Z82	ZSSHNRRLRTA		3.4	
Z21 (HAX42)	ZSDHALGTNLRSDNAKEPGDYNCCGNGNSTGRKVFNRRRPSAIPT	11.27	0.7	

FIG.10B

SN:10

Peptide Name	Sequence	pI	IC_{50}	GST/C2BBel
ELAN016 (SNi10)	RVGQCTDSDVRRPWARSCAHQGCGAGTRNSHGCITRPLRQASAH	10 19	0.22	++
116	RVGQCTDSDVRRPWARSCA			-
117	VRRPWARSCAHQGCGAGTRNS			+
118	GTRNSHGCITRPLRQASAH			+/-
Z17	ZRVGQCTDSDVRRPWARSCAH	8.66	3.6	
Z16C23	ZCGAGTRNSHGCITRPLRQASAH	9.03	0.7	
Z36	ZVRRPWARSCAHQGCGAGTRNS	11.62	0.27	
Z37	ZCTDSDVRRPWARSC	8.01	3	

Peptide Name	Sequence	pI	IC_{50}	GST/C2BBel
ELAN021(HAX42)	SDHALGTNLRSDNAKEPGDYNCCGNGNSTGRKVFNRRRPSAIPT	11 27	5.5	++
ELAN018(PAX2)	STPPSREAYSRPYSVDSDSDTNAKHSSHNRRLRTRSRPNG	10.88	0.23	+++
Z26	ZSEANLDGRKSRYSSPRRNSSTRPRTSPNSVHARYPSTDHD	10.88	<0.2	
Z38	ZSRANTDGRKSRYSSPRRNSSTEPRLSPNSVHARYPSTDHD	10.88	<0.2	
Z34 (PAX2 14mer)	ZSSHNRRLRTRSRPN	12.7	0.33	

FIG.10C

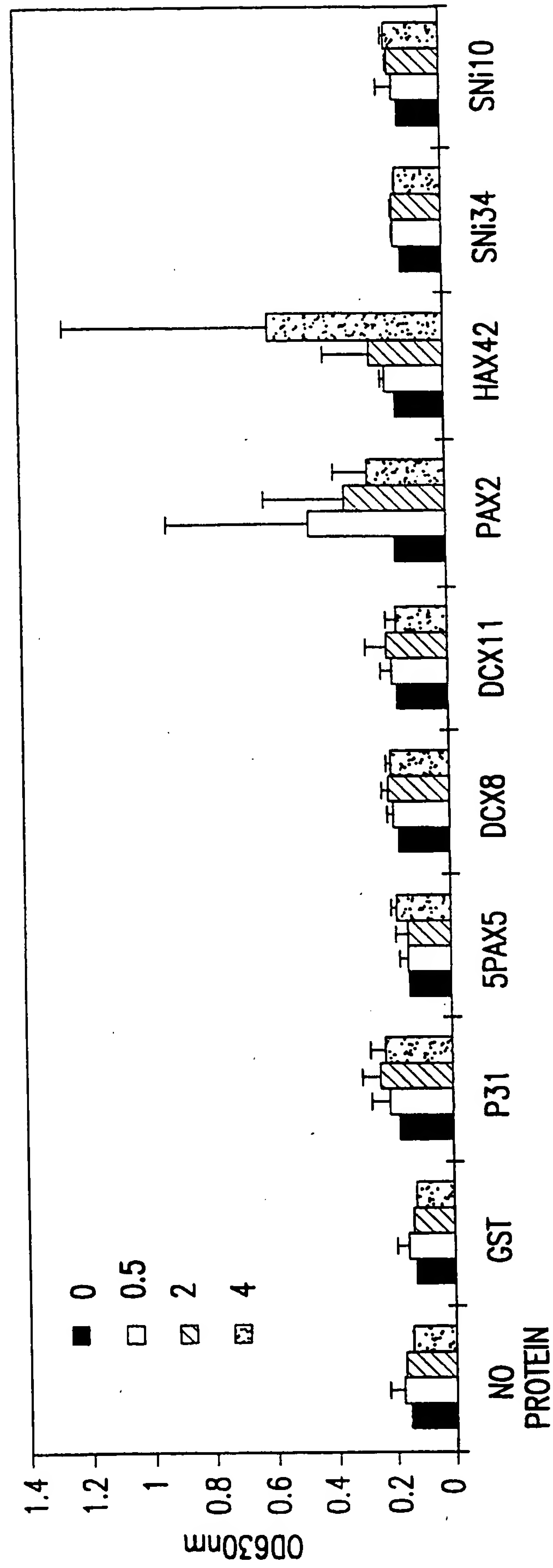

OD630nm
0
0.2
0.4
0.6
0.8
1
1.2
1.4
0
0.5
2
4
NO PROTEIN
GST
P31
5PAX5
DCX8
DCX11
PAX2
HAX42
SNi34
SNi10

FIG.11A

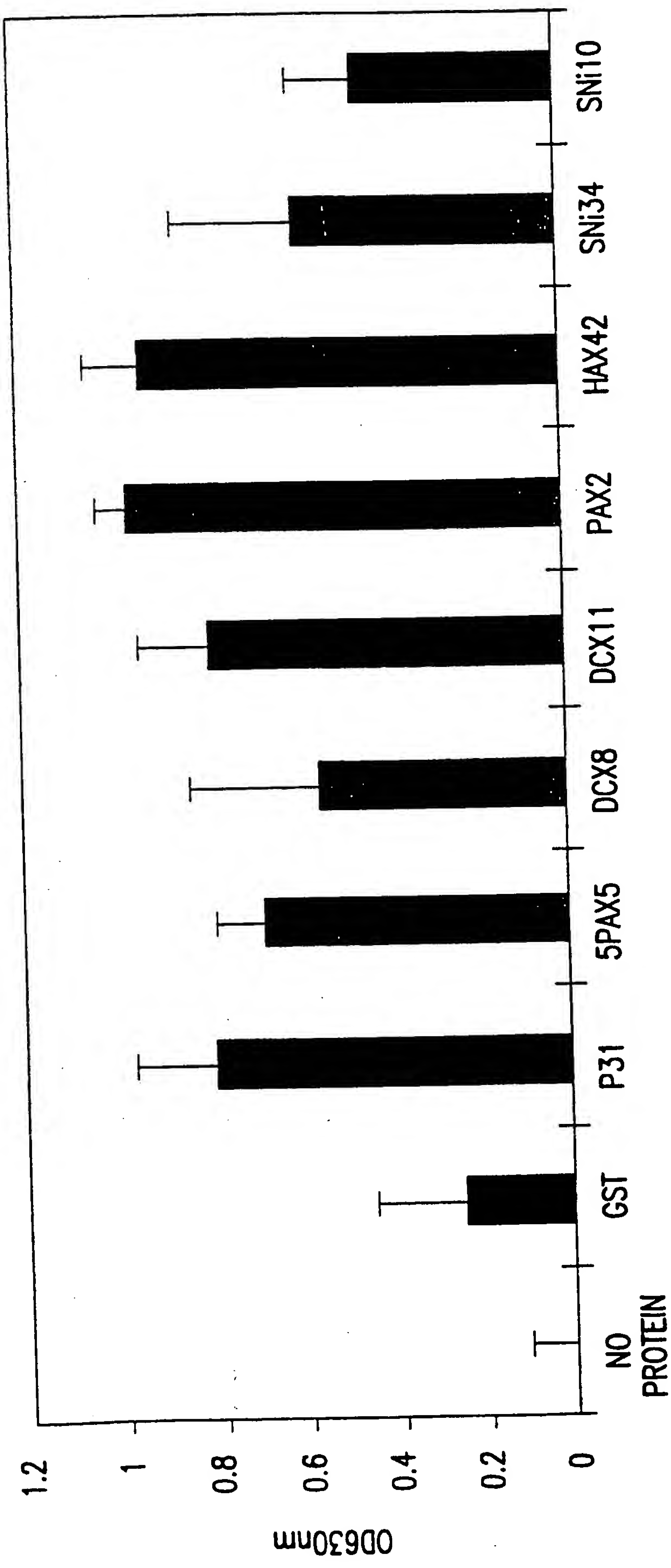

OD630nm
0
0.2
0.4
0.6
0.8
1
1.2
NO PROTEIN
GST
P31
5PAX5
DCX8
DCX11
PAX2
HAX42
SNi34
SNi10

FIG.11B

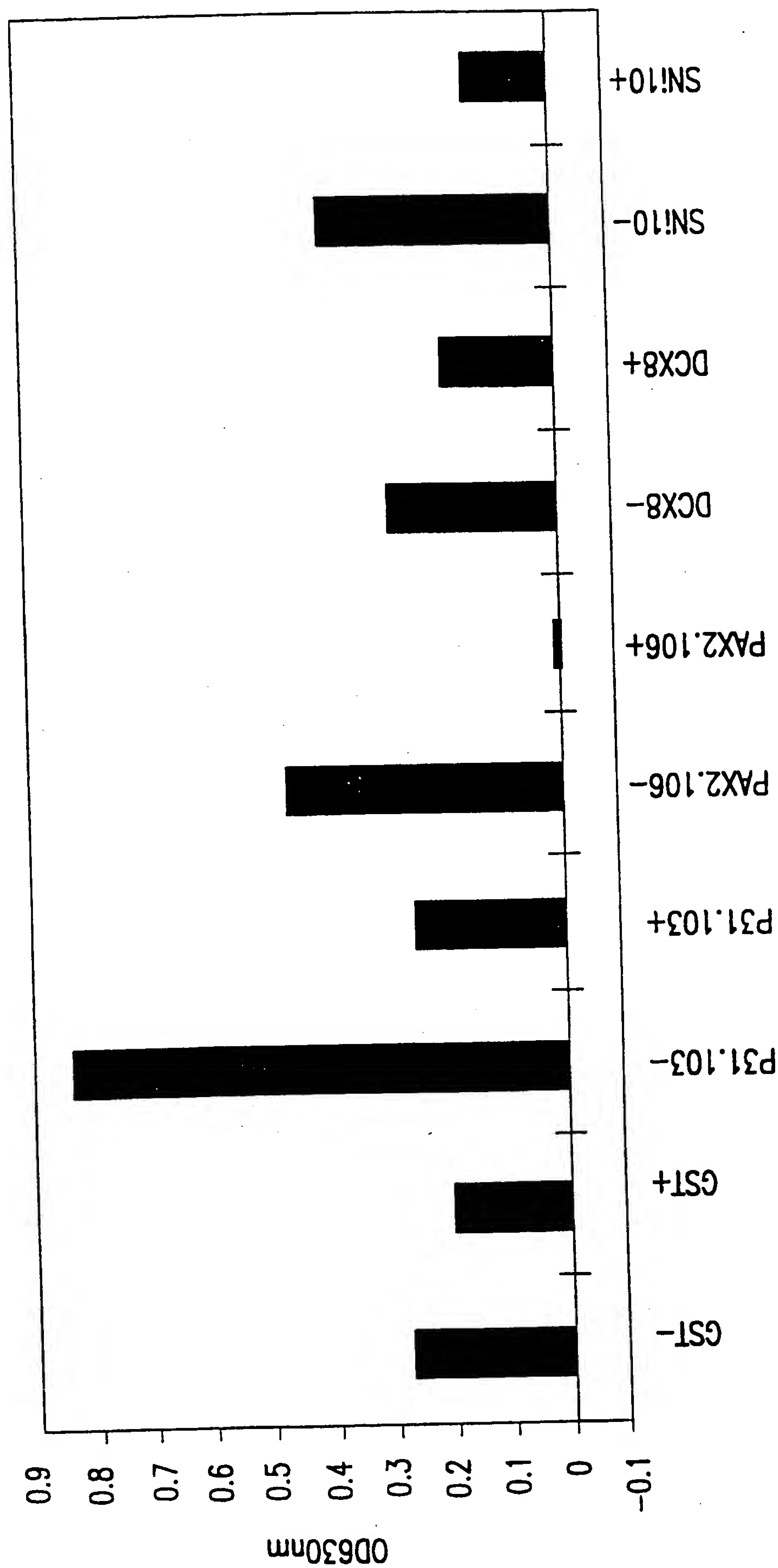

OD630nm
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
GST-
GST+
P31.103-
P31.103+
PAX2.106-
PAX2.106+
DCX8-
DCX8+
SNi10-
SNi10+

FIG.12

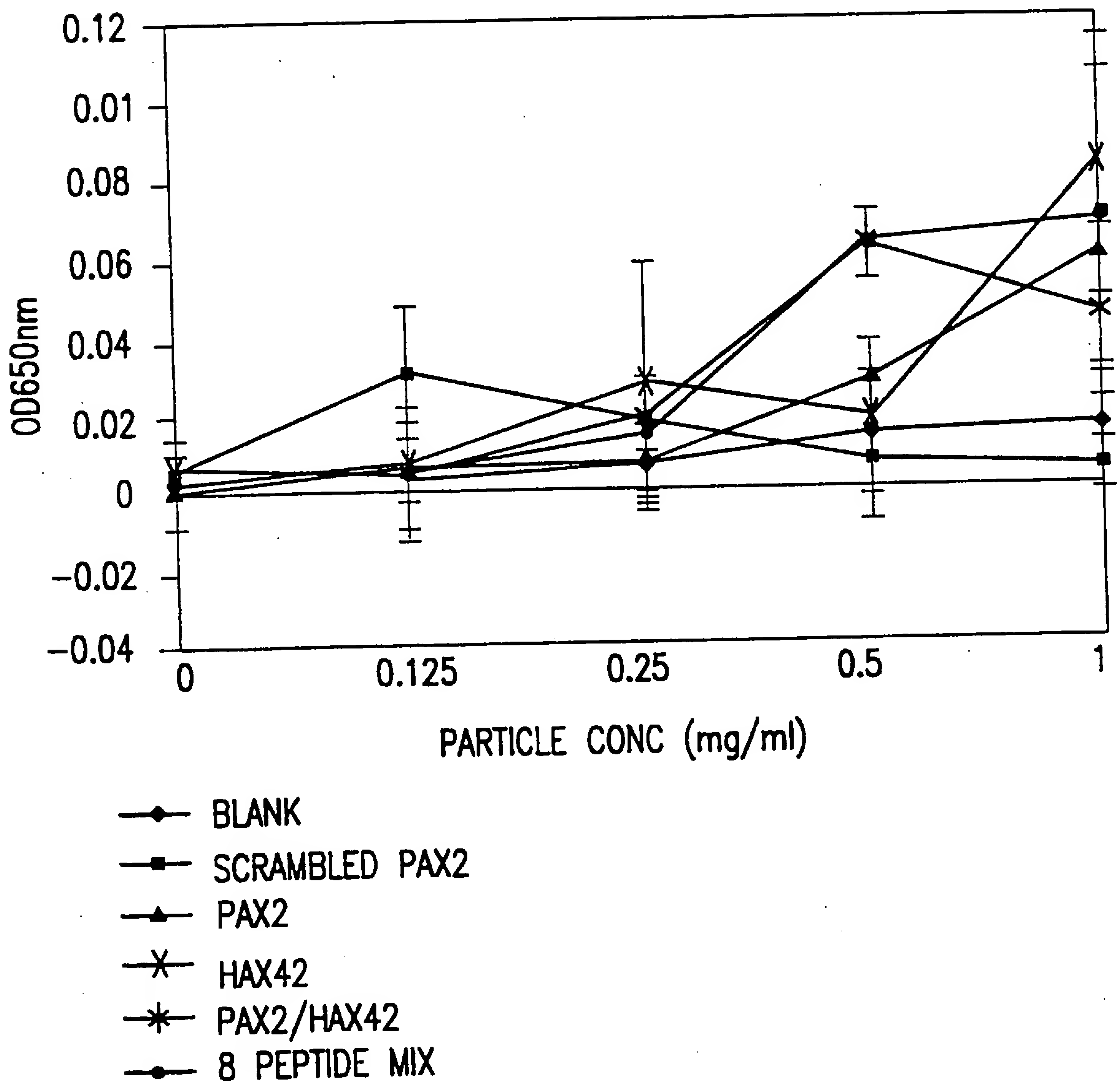
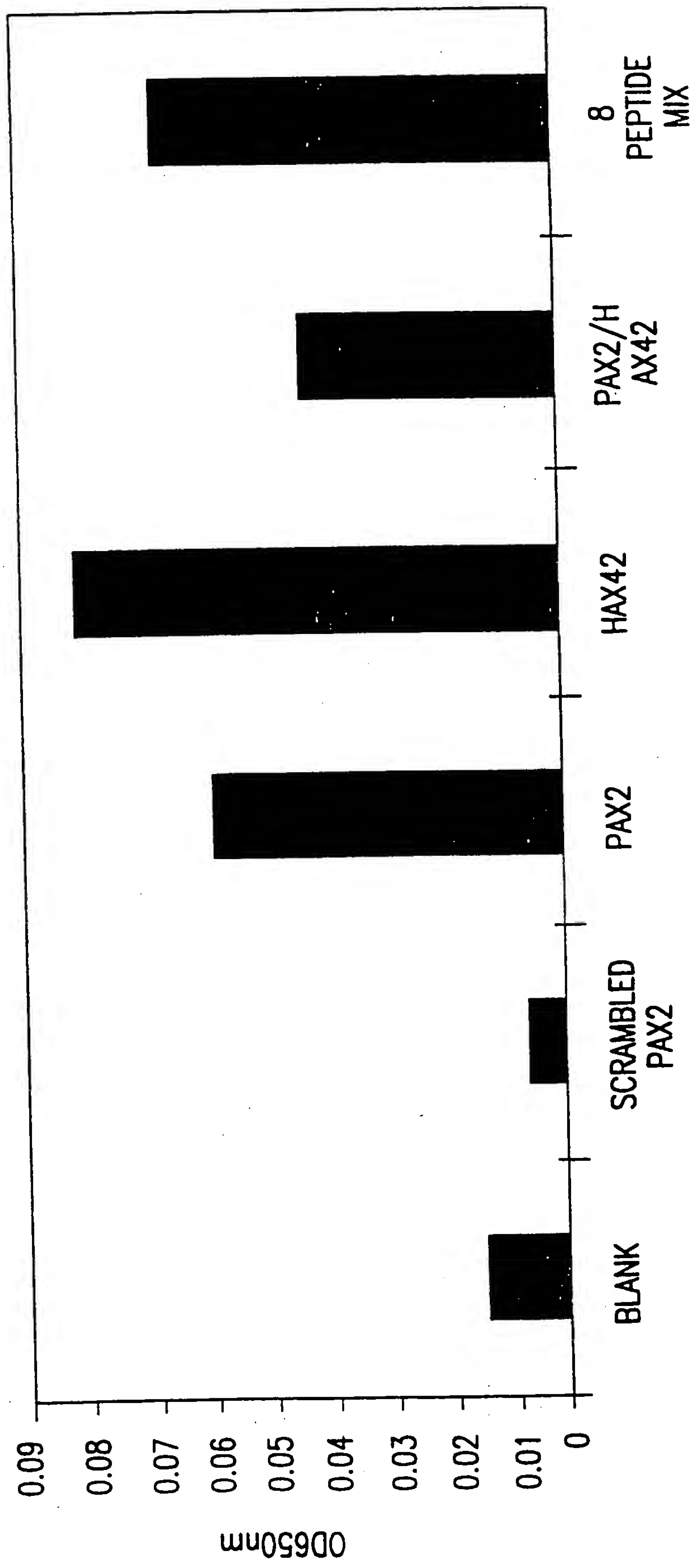

0.12
0.01
0.08
0.06
0.04
0.02
0
−0.02
−0.04
OD650nm
0
0.125
0.25
0.5
1
PARTICLE CONC (mg/ml)
BLANK
SCRAMBLED PAX2
PAX2
HAX42
PAX2/HAX42
8 PEPTIDE MIX

FIG.13A



OD650nm
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
BLANK
SCRAMBLED PAX2
PAX2
HAX42
PAX2/HAX42
8 PEPTIDE MIX

FIG.13B

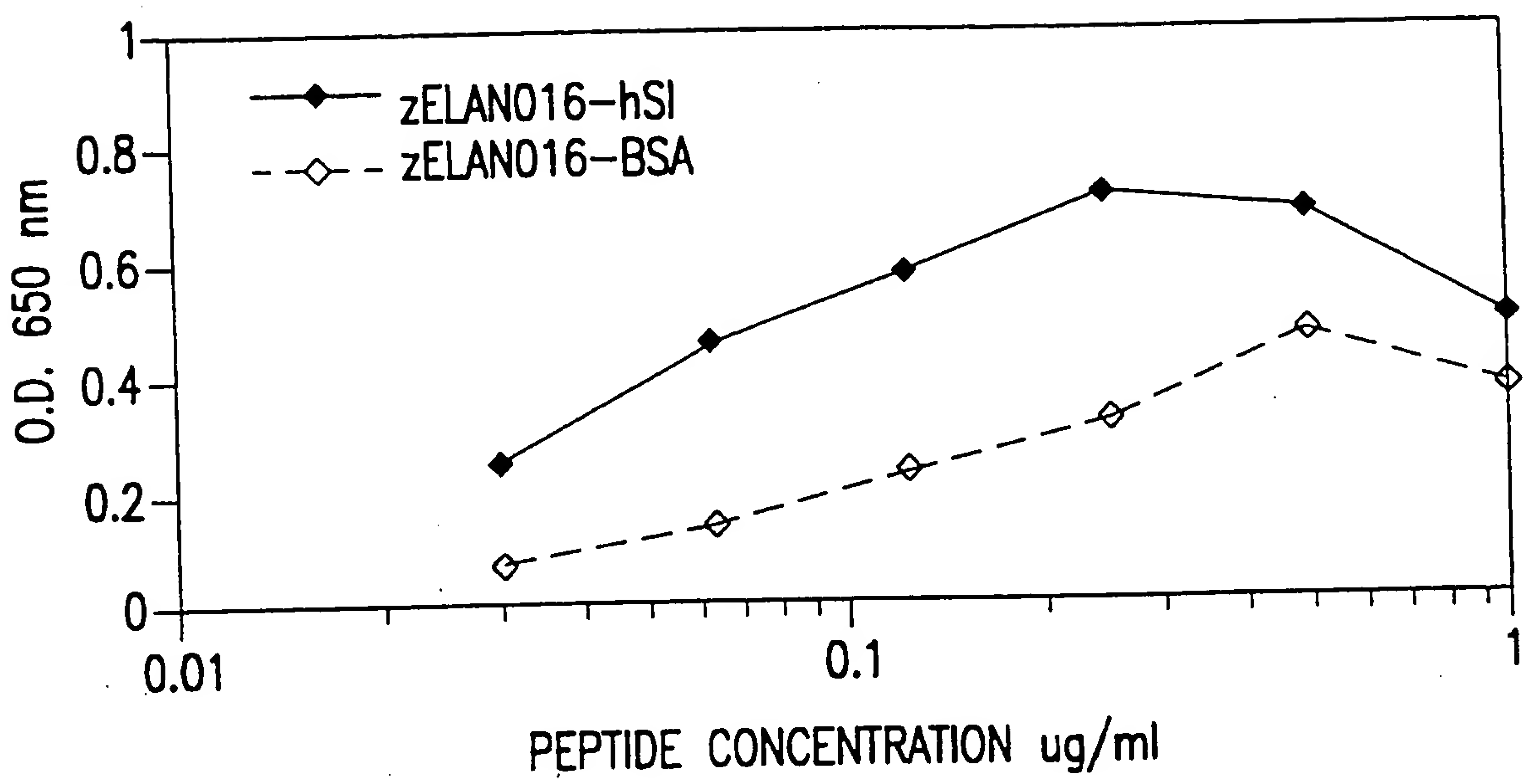


FIG. 14A

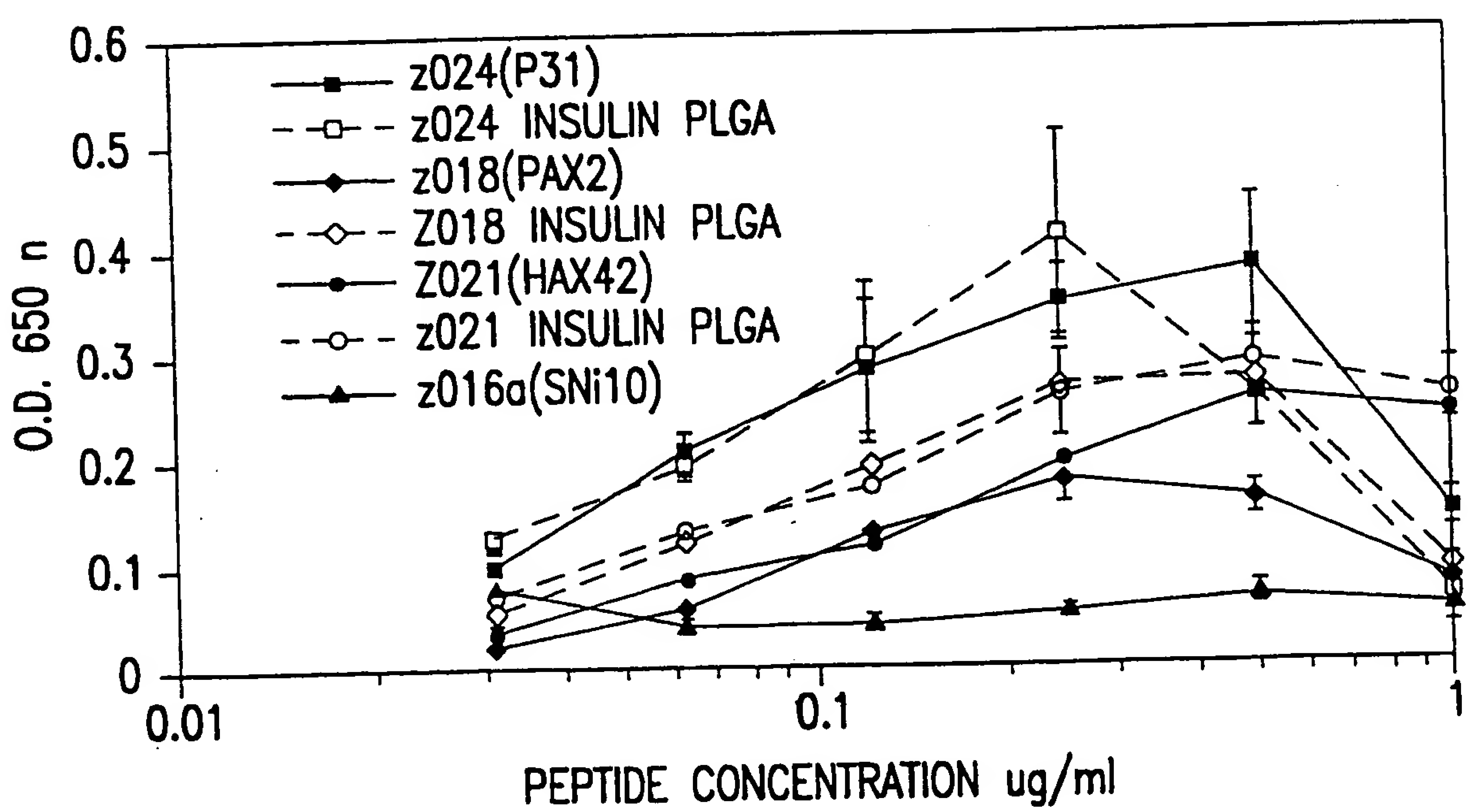
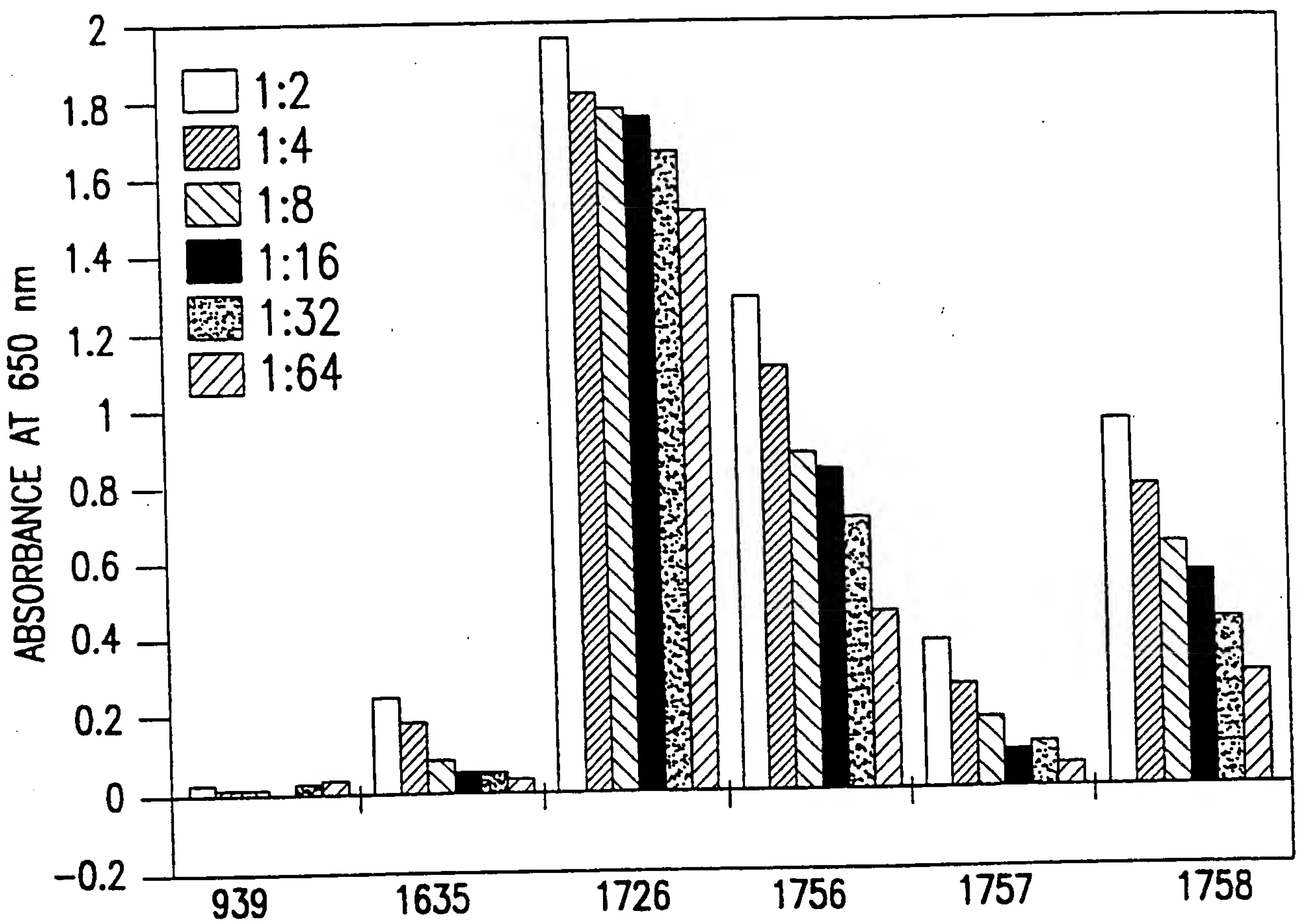


FIG. 14B



ABSORBANCE AT 650 nm
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
1:2
1:4
1:8
1:16
1:32
1:64
939
1635
1726
1756
1757
1758

FIG. 15A

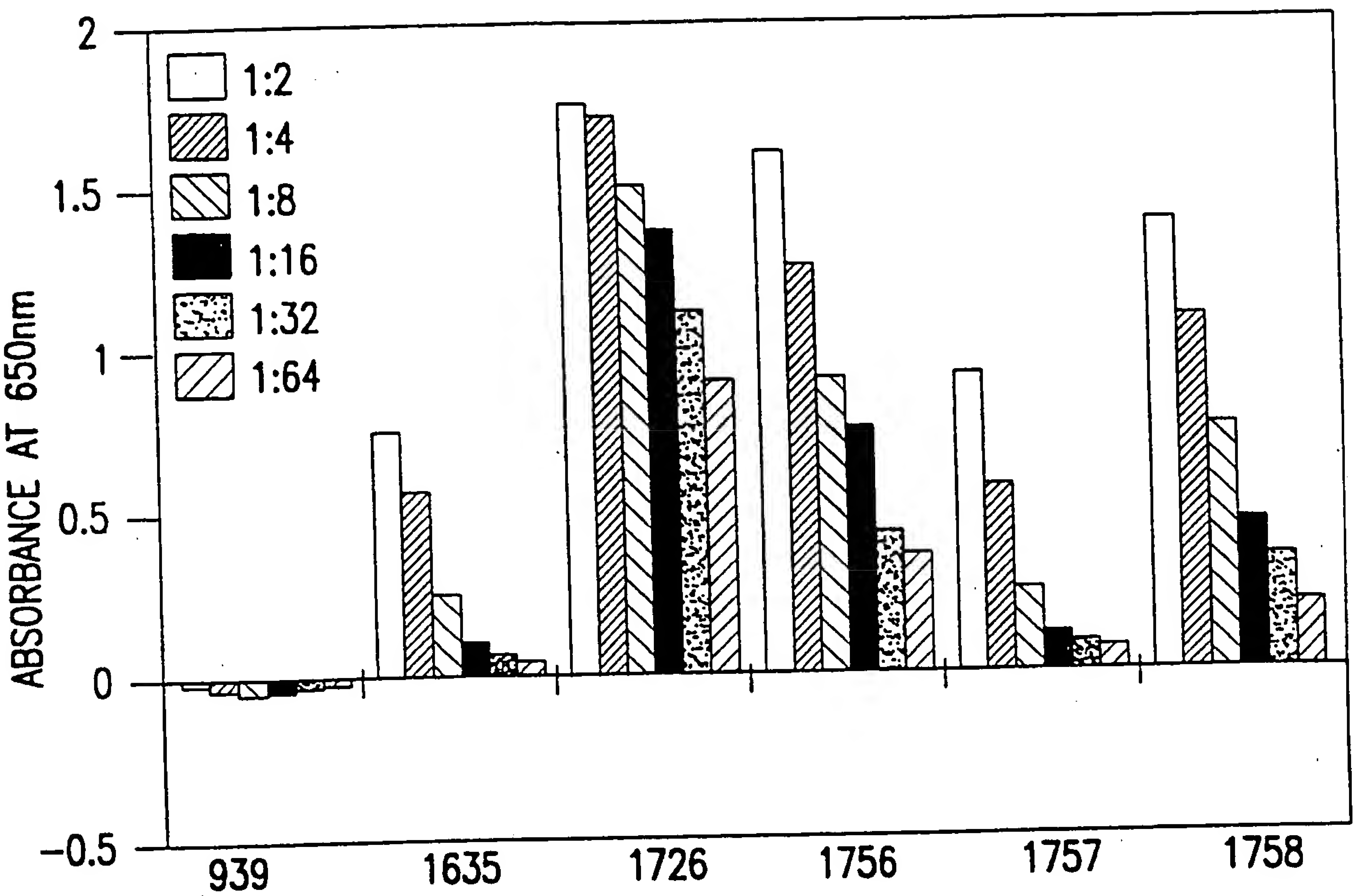
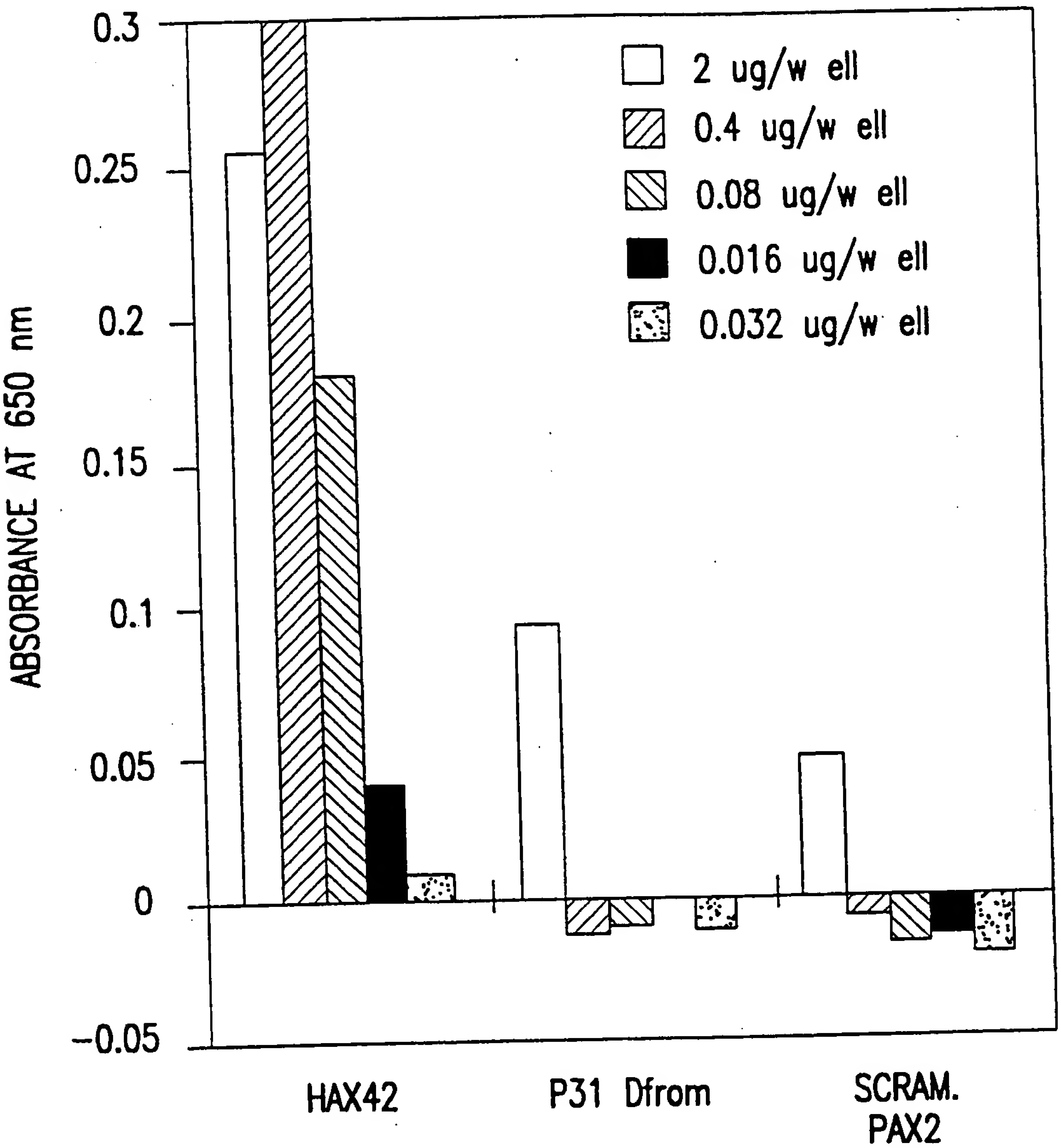
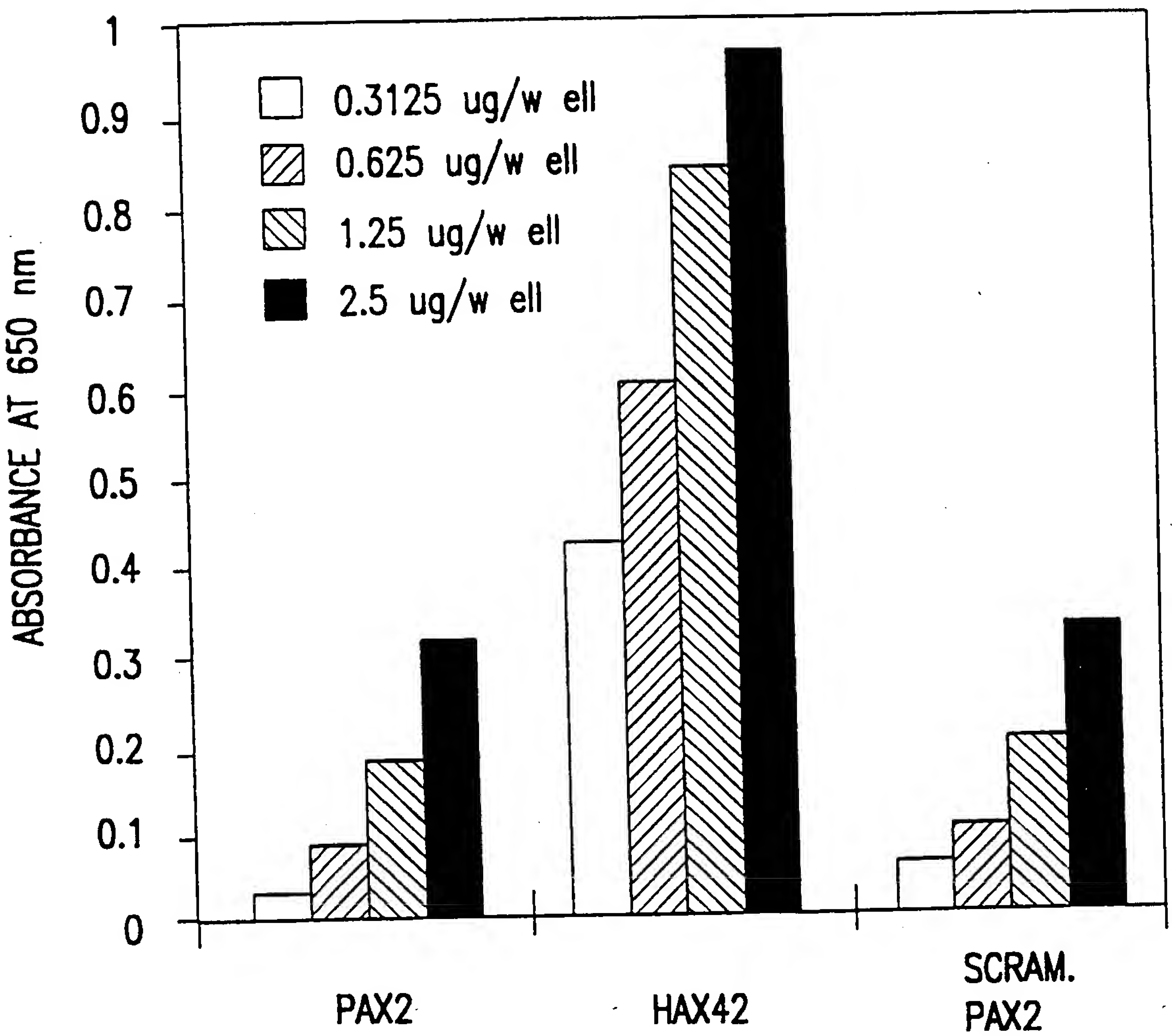

2
1.5
1
0.5
0
-0.5
ABSORBANCE AT 650nm
1:2
1:4
1:8
1:16
1:32
1:64
939
1635
1726
1756
1757
1758

FIG. 15B



0.3
0.25
0.2
0.15
0.1
0.05
0
-0.05
ABSORBANCE AT 650 nm
2 ug/w ell
0.4 ug/w ell
0.08 ug/w ell
0.016 ug/w ell
0.032 ug/w ell
HAX42
P31 Dfrom
SCRAM. PAX2

FIG.16A



ABSORBANCE AT 650 nm
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.3125 ug/w ell
0.625 ug/w ell
1.25 ug/w ell
2.5 ug/w ell
PAX2
HAX42
SCRAM. PAX2

FIG.16B

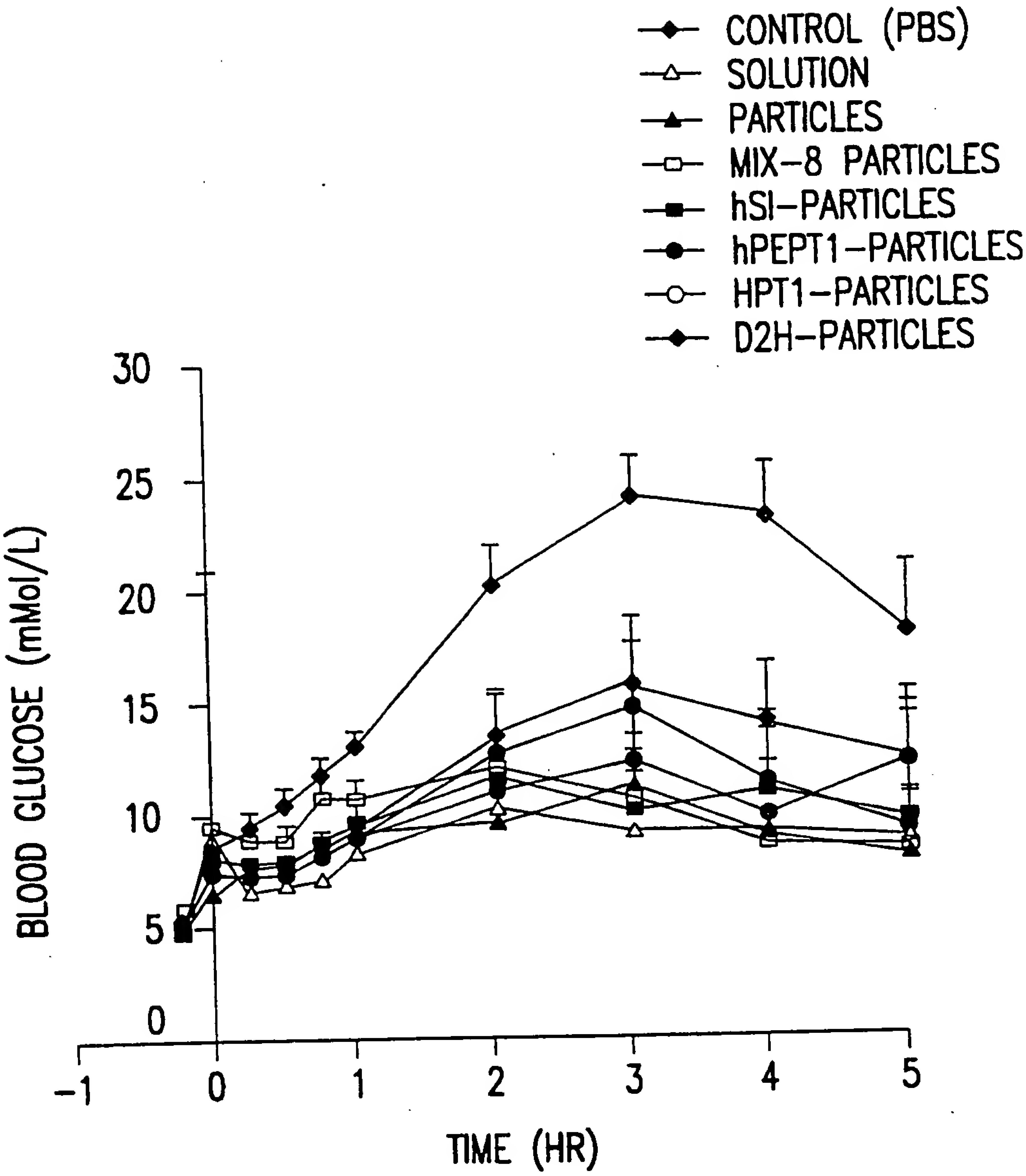

CONTROL (PBS)
SOLUTION
PARTICLES
MIX-8 PARTICLES
hSI-PARTICLES
hPEPT1-PARTICLES
HPT1-PARTICLES
D2H-PARTICLES
BLOOD GLUCOSE (mMol/L)
TIME (HR)
30
25
20
15
10
5
0
-1
0
1
2
3
4
5

FIG. 17A

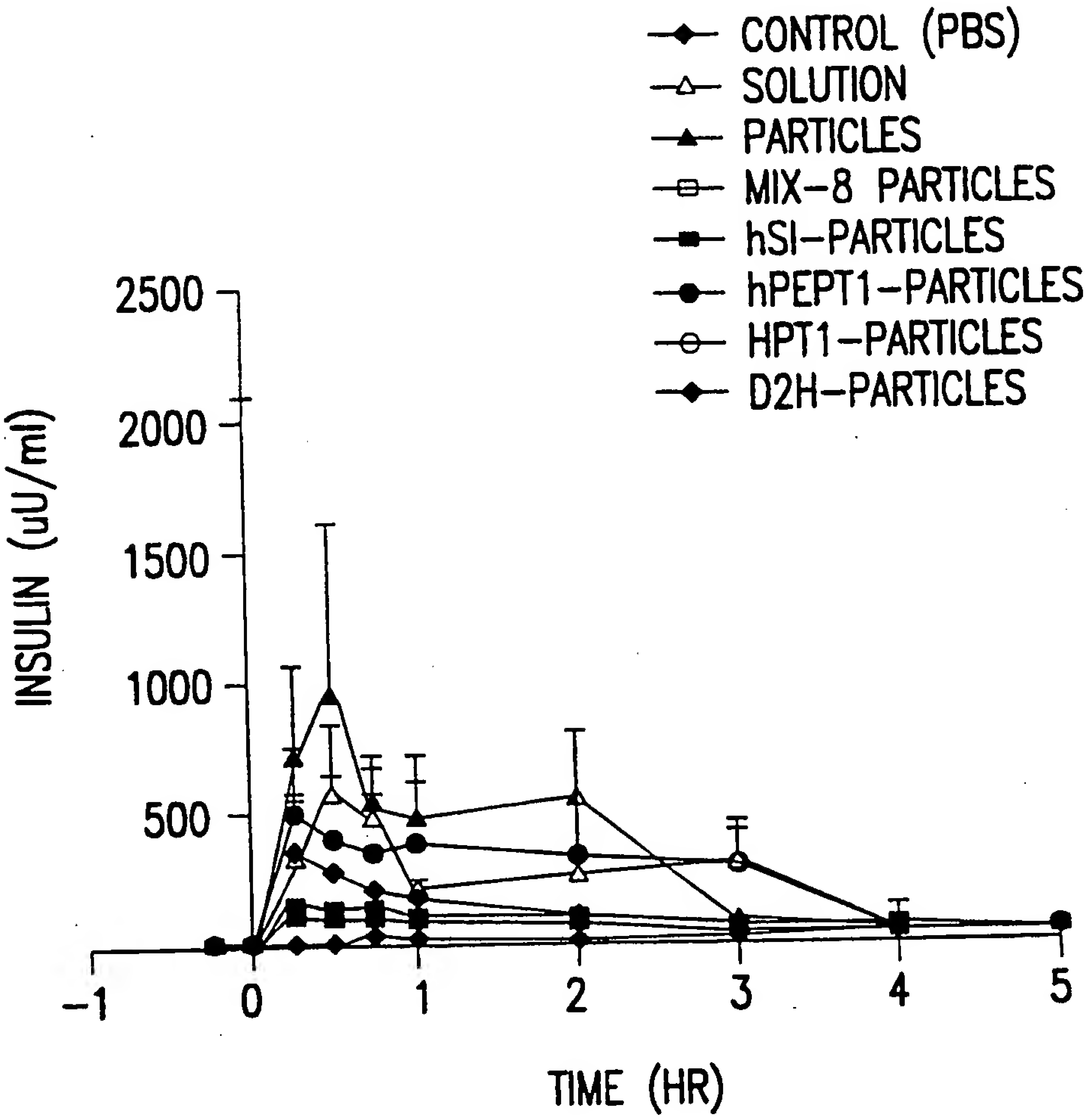

CONTROL (PBS)
SOLUTION
PARTICLES
MIX-8 PARTICLES
hSI-PARTICLES
hPEPT1-PARTICLES
HPT1-PARTICLES
D2H-PARTICLES
INSULIN (uU/ml)
2500
2000
1500
1000
500
-1
0
1
2
3
4
5
TIME (HR)

FIG. 17B

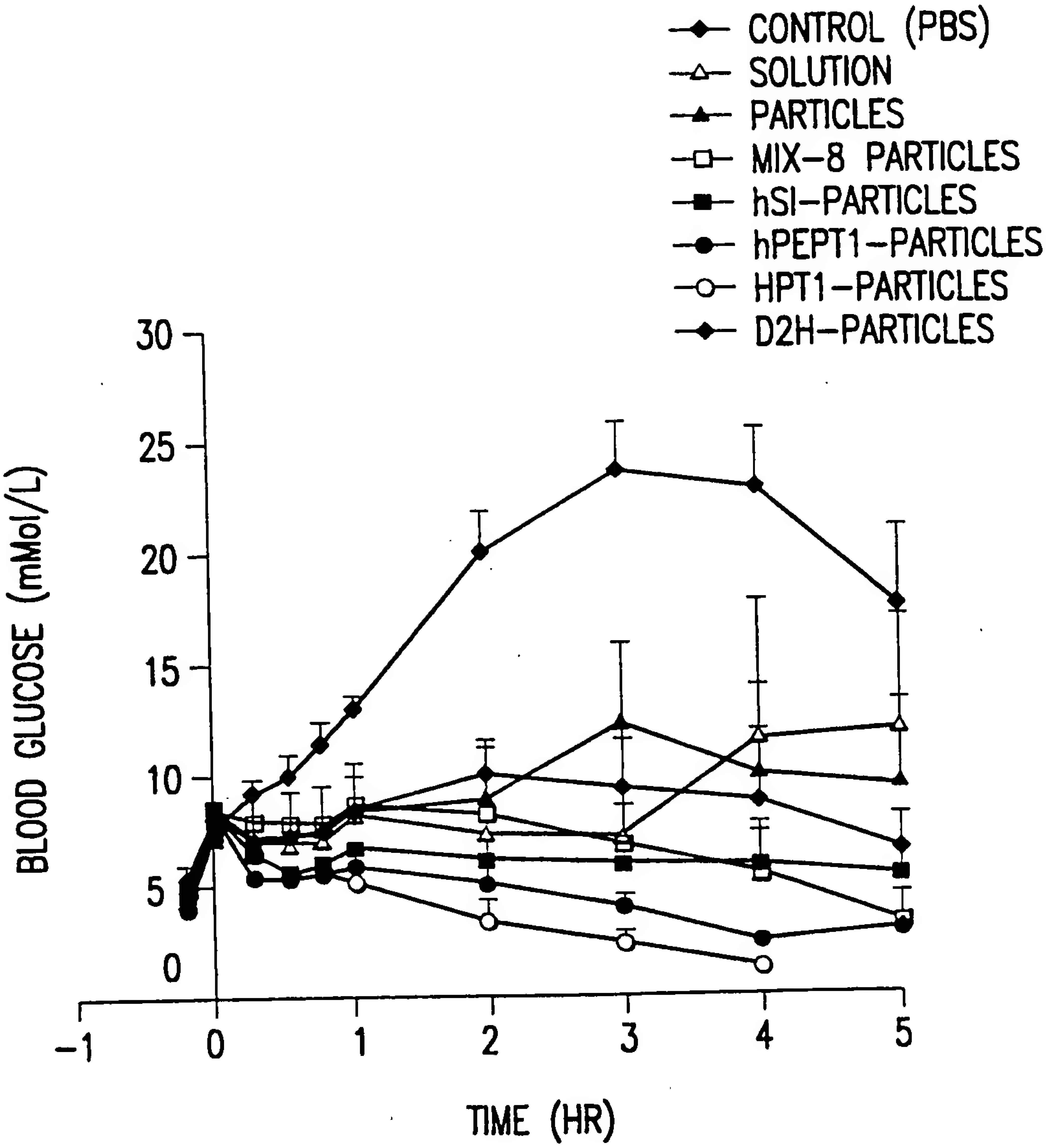

CONTROL (PBS)
SOLUTION
PARTICLES
MIX-8 PARTICLES
hSI-PARTICLES
hPEPT1-PARTICLES
HPT1-PARTICLES
D2H-PARTICLES
BLOOD GLUCOSE (mMol/L)
30
25
20
15
10
5
0
-1
0
1
2
3
4
5
TIME (HR)

FIG. 18A

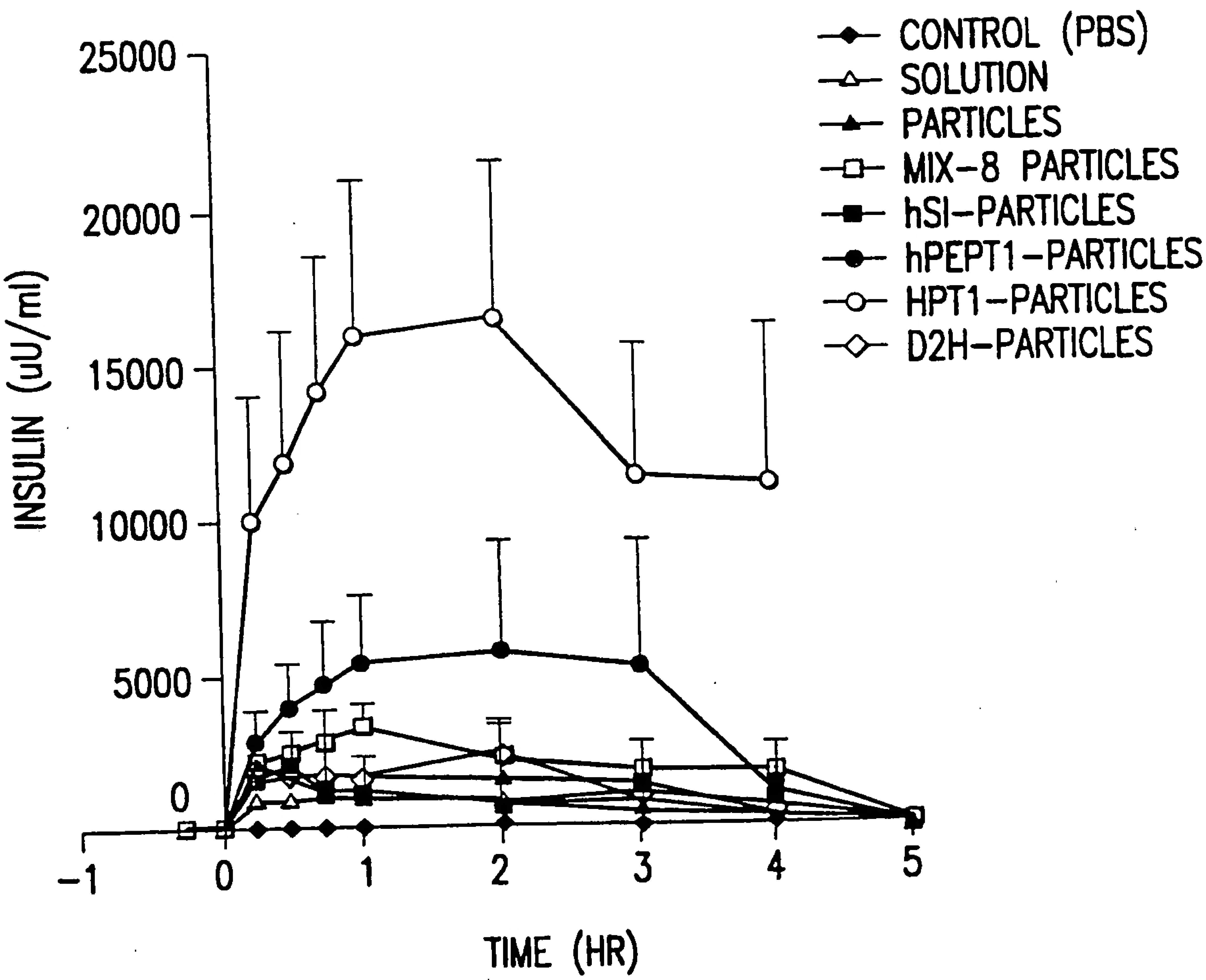

25000
20000
15000
10000
5000
0
INSULIN (uU/ml)
-1
0
1
2
3
4
5
TIME (HR)
CONTROL (PBS)
SOLUTION
PARTICLES
MIX-8 PARTICLES
hSI-PARTICLES
hPEPT1-PARTICLES
HPT1-PARTICLES
D2H-PARTICLES

FIG.18B

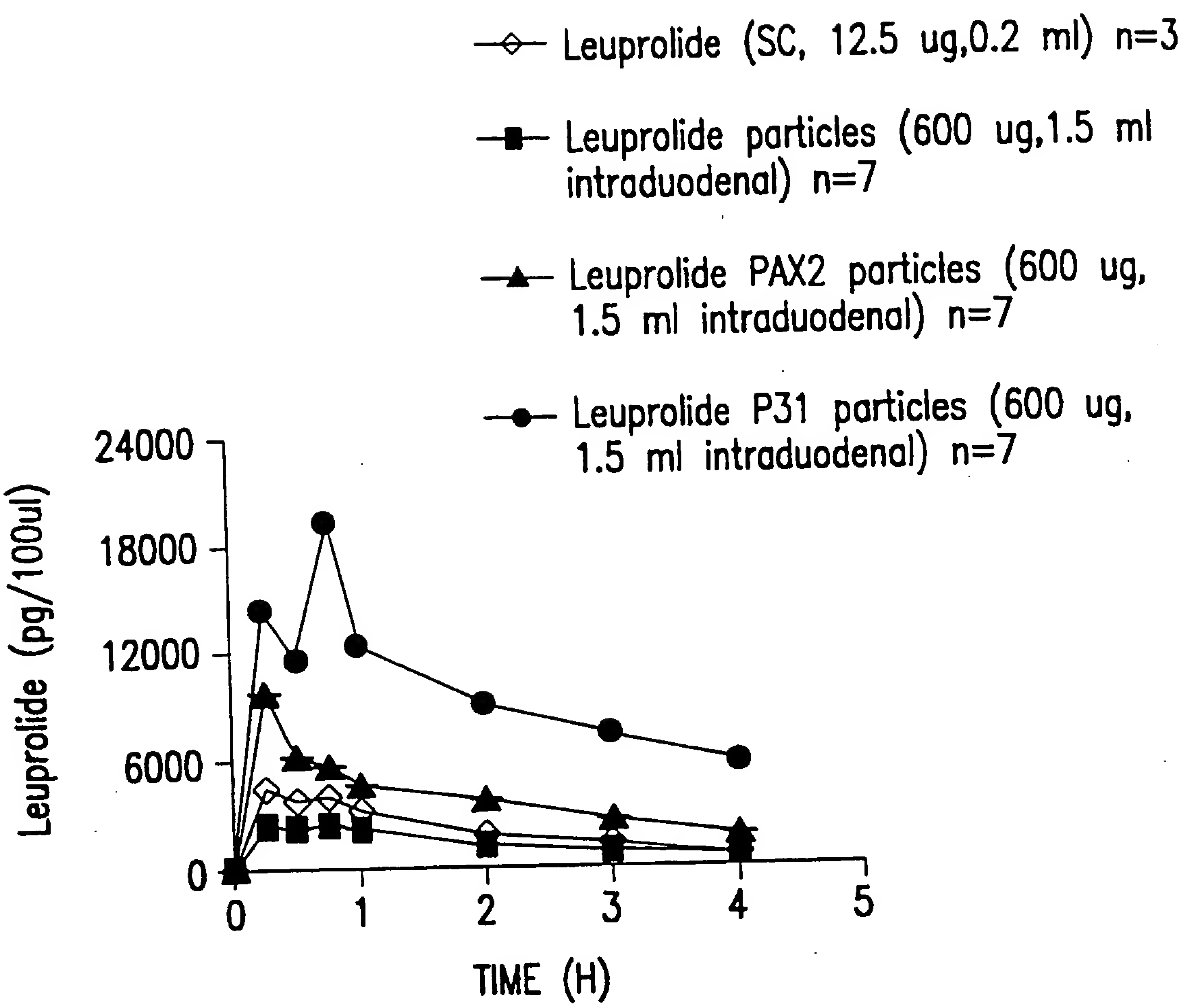

Leuprolide (SC, 12.5 ug,0.2 ml) n=3
Leuprolide particles (600 ug,1.5 ml intraduodenal) n=7
Leuprolide PAX2 particles (600 ug, 1.5 ml intraduodenal) n=7
Leuprolide P31 particles (600 ug, 1.5 ml intraduodenal) n=7
Leuprolide (pg/100ul)
24000
18000
12000
6000
0
0
1
2
3
4
5
TIME (H)

FIG. 19

P31 AA SEQ. POSITION	KNOWN PROTEIN	HOMOLOGOUS SEQ. POSITION
12-34	FASCICULIN 2	10-32
4-12	MESENTERICOPEPTIDASE	54-62
15-31		175-191
26-39	CORE PROTEIN (HEPATITIS C VIRUS)	5-18
26-39		11-24
26-39		21-34
26-39		38-51
23-30		39-55
25-39		41-55
26-39		51-64
16-39	PT-NANBH POLYPROTEIN N-TERMINUS	51-64
28-40	AL2 PROTEIN (CAENORHABDITISELEGANS)	70-82
26-38	CAPSID PROTEIN (HEPATITIS C VIRUS TYPE 3g)	48-60
26-39	GENOME POLYPROTEIN (HEPATITIS C VIRUS)	57-70

FIG.20

DCX8AA SEQ. POSITION	KNOWN PROTEIN	HOMOLOGOUS SEQ. POSITION
20-27	ENDO-1,4-BETA-D-GLUCANASE	78-85
30-37		221-228
21-34	P-HYDROXYBENZOATE HYDROXYLASE	285-298
5-15		54-64
7-21	CYTOCHROME	50-64
7-21	CYTOCHROME C3	50-64
	TRIMETHYLARNINE DEHYDROGENASE	208-219
32-43		396-407
30-37	Gag-JunD FUSION PROTEIN	24-31
26-30		16-20
23-44	SECRETIN PRECURSOR, N-PROSECRITIN, SECRITIN AINIDE	18-39
33-44	T-CELL RECEPTOR V BETA CHAIN	15-26
27-33		3-9
23-44	SECRETIN PRECURSOR PIR	18-39
31-44	HYPOTHETICAL PROTEIN V (SYNECHOCYSTIS)	275-288
24-30		251-257
23-43	PUTATIVE RNA BINDING PROTEIN	230-250
28-40	Mu SON OF SEVENLESS 1	1-13
24-35	NEUROPEPTIDE PRECURSOR	80-91
29-43		5-19
23-43	RNA-BINDING PROTEIN (MACACAFASCICULARIS)	230-250
23-43	RNA-BINDING PROTEIN (HOMOSAPIENS)	230-250
23-43	AUTOSOMAL GENE-AZOOSPERMIA FACTOR	230-250
25-38	COLLAGEN	25-28
24-35		4-15
29-41	PROBABLE CELL GROWTH REGULATOR	306-318
24-35	RIBOSOMAL PROTEIN S2	24-35
T6-39		182-185
24-44	CAENORHABDITIS ELEGANS	296-316
23-34	pid:e208155 (HOMO SAPIENS)	61-72
36-43		116-123

FIG.21A

DCX8A SEQ. POSITION	KNOWN PROTEIN	HOMOLOGOUS SEQ. POSITION
24-38	XYLULOSE KINASE	16-30
24-39	CAENORHABDITIS ELEGANS	57-72
26-42		65-81
27-33	HYPOTHETICAL PROTEIN-PHAGE BZ13	22-28
35-39		31-35
30-42	CEREBELLIN-LIKE GLYCOPROTEIN	2-14
8-22	DNA PRIMASE	170-184
2-7		76-81
5-21	COAT PROTEIN (BEAN COMMON MOSAIC VIRUS)	12-28
5-21	COAT PROTEIN (BEAN COMMON MOSAIC VIRUS)	33-49
5-21		19-35
5-21	POLYPROTEIN (BEAN COMMON MOSAIC VIRUS)	215-231
5-21		39-55
5-21	Nib PROTEINLCOAT PROTEIN (COWPEA APHID-BOME MOSAIC VIRUS)	92-108
2-13	MHC CLASS 1 PIPI (PITHECIA)	111-122
14-22		236-334
3-19	TALIN (CAENORHABDITIS ELEGANS)	1538-1554
2-9	ACETAMIDASE PIR	359-366
9-20		483-494
10-16	RHIZOBIONS ETLI STRAIN	134-140
17-30		173-186
31-39		200-208
2-11	NEUROTOXIN 1 (TOXIN B) A. STOKESI	7-16
12-33		26-47
21-27	SUID HERPES VIRUS 1 EARLY PROTEIN	425-432
30-43		51-64
13-42	RICE cDNA PARTIAL SEQUENCE	50-151
8-15	FUSION PROTEIN	24-31
4-8		16-20
1-22	SECRETIN PRECURSOR, N-PROSECRETIN, SECRETIN-AMIDE	18-39
11-22	T-CELL RECEPTOR V BETA CHAIN	15-26
5-11		3-9
9-22	HYPOTHETICAL PROTEIN	275-288
2-8		251-257

FIG.21B

DCX8A SEQ. POSITION	KNOWN PROTEIN	HOMOLOGOUS SEQ. POSITION
1-21	PUTATIVE RNA BINDING PROTEIN	230-250
6-18	HYPOTHETICAL PROTEIN-MOUSE PIR	1-13
2-13	NEUROPEPTIDE PRECURSOR	80-91
7-21	orf3-HUMAN	5-19
1-21	RNA-BINDING PROTEIN	230-250
13-16	COLLAGEN	25-28
7-19	PROBABLE CELL GROWTH OR DIFFERENTIATION REGULATOR	306-318
2-13	RIBOSOMAL PROTEIN S2	14-25
14-17		182-185
2-22	CAENORHABDITIS ELEGANS	296-316
1-12	HOMOSAPIENS	61-72
14-21		116-123
2-16	XYLULOSE KINASE	16-30
8-15	T CELL RECEPTOR DELTA CHAIN	55-62
5-8		12-15
8-17	SEQ. 43 FROM PATENT US	12-21

FIG.21C

DAB10 AA SEQ. POSITION	KNOWN PROTEIN	HOMOLOGOUS SEQ. POSITION
13-34	1,3-BETA-GLLUCANASE	231-252
3-11	PHOTOSYNTHETIC REACTION CENTER	20-28
16-27		128-139
28-35	MYB PROTO-ONCOGENE PROTEIN	131-138
5-18		32-45
23-36	LYSOZYME MUTANT	130-143
28-35	LIPASE	400-407
3-15		159-171
3-37	TRYPSIN	169-203
13-34	1,3-1,4-BETA-GLUCANASE	232-253
4-10	LACTATE DEHYDROGENASE	190-196
11-7		244-250
4-10	APO-LACTATE DEHYDROGENASE	190-196
11-17		244-250
4-10	LACTATE DEHYDROGENASE	191-197
11-17		245-251
16-26	OVOTRANSFERRIN	240-250
23-36	GENOME POLYPROTEIN MATRIX PROTEIN	1022-1035
14-20	ROUS SARCOMA VIRUS	43-49
2-12		13-23
14-20	HYPOTHETICAL PROTEIN-AVIAN LEUKOSIS VIRUS	43-49
4-20	T CELL RECEPTOR DELTA CHAIN VARIABLE REGION	1-4
14-18		12-16
2-12	GAG POLYPROTEIN-AVIAN ENDOGENOUS VIRUS RAV-0	139-149
14-20		169-175
	p19 PROTEIN-AVIAN ERYTHROBLASTOSIS VIRUS	189-199
14-20		219-225
7-19	ALI PROTEIN-POTATO YELLOW MOSAIC VIRUS	222-234
3-22	ENDO-1,4-BETA GLUCANASE	186-205
6-18	I a PROTEIN-BROME MOSAIC VIRUS	430-442
2-12	GAG POLYPROTEIN-FUJINAMI SARCOMA VIRUS	186-196
14-22		216-222
2-12	GAG PROTEIN-ROUS SARCOMA VIRUS	190-200
14-20		220-226
1-12	CORTICOTROPIN-LIKE INTERMEDIATE LOBE PEPTIDE	7-18
1-22	GENE PRODUCT (CAENORHABDITIS ELEGANS)	4-25
31-37	T CELL RECEPTOR DELTA CHAIN	56-62
26-39		12-15
26-37	LYSOZYME MUTANT	133-144

FIG.22

ATG TCC CCT ATA CTA GGT TAT TGG AAA ATT AAG GGC CTT GTG CAA CCC 48
Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1 5 10 15

ACT CGA CTT CTT TTG GAA TAT CTT GAA GAA AAA TAT GAA GAG CAT TTG 96
Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
20 25 30

TAT GAG CGC GAT GAA GGT GAT AAA TGG CGA AAC AAA AAG TTT GAA TTG 144
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
35 40 45

GGT TTG GAG TTT CCC AAT CTT CCT TAT TAT ATT GAT GGT GAT GTT AAA 192
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
50 55 60

TTA ACA CAG TCT ATG GCC ATC ATA CGT TAT ATA GCT GAC AAG CAC AAC 240
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65 70 75 80

ATG TTG GGT GGT TGT CCA AAA GAG CGT GCA GAG ATT TCA ATG CTT GAA 288
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85 90 95

GGA GCG GTT TTG GAT ATT AGA TAC GGT GTT TCG AGA ATT GCA TAT AGT 336
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100 105 110

AAA GAC TTT GAA ACT CTC AAA GTT GAT TTT CTT AGC AAG CTA CCT GAA 384
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115 120 125

ATG CTG AAA ATG TTC GAA GAT CGT TTA TGT CAT AAA ACA TAT TTA AAT 432
Met Leu Lys Met Phe GlU Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130 135 140

GGT GAT CAT GTA ACC CAT CCT GAC TTC ATG TTG TAT GAC GCT CTT GAT 480
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145 150 155 160

GTT GTT TTA TAC ATG GAC CCA ATG TGC CTG GAT GCG TTC CCA AAA TTA 528
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165 170 175

GTT TGT TTT AAA AAA CGT ATT GAA GCT ATC CCA CAA ATT GAT AAG TAC 576
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180 185 190

TTG AAA TCC AGC AAG TAT ATA GCA TGG CCT TTG CAG GGC TGG CAA GCC 624
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
195 200 205

ACG TTT GGT GGT GGC GAC CAT CCT CCA AAA TCG GAT CTG GTT CCG CGT 672
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
210 215 220

GGA TCC CCA GGA ATT CCC GGG TCG ACT CGA GCG GCC GCA TCG TGA 717
Gly Ser Pro Gly Ile Pro Gly Ser Thr Arg Ala Ala Ala Ser
225 230 235

FIG.23